PARTIAL SYNTHESIS OF C-20 GIBBERELLINS

A Thesis Submitted for the Degree of Doctor of Philosophy

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by David J. Owen

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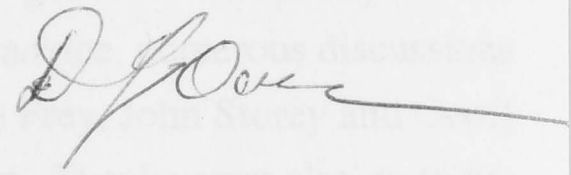
DECLARATION

This thesis contains no material previously submitted for a degree in any other University, and to the best of my knoweledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.



David James Owen

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ABSTRACT

This thesis describes the partial synthesis of C-20 gibberellins including C-20 methyl derivatives in order to confirm the structures of numerous putative structural assignments given to natural extracts.

Chapter One contains a brief survey of research into gibberellins, including the history, biosynthesis, and the previously reported partial synthesis of key gibberellin intermediates required for this work.

Chapter Two details the methodology for the reduction of the C-20 aldehyde function in the protected derivative of GA_{19} **24** to produce the desired C-20 methyl gibberellin GA_{53} **62**. This result was achieved *via* a Wolff-Kishner reduction of the C-20 aldehyde of GA_{19}, and represents the first partial synthesis of a C-20 methyl gibberellin from the freely available fungal gibberellin, gibberellic acid.

Chapter Three deals with the extention of the C-20 gibberellin methodology with the production of the methyl esters of three synthetic 15β-hydroxy C-20 gibberellins; 15β-hydroxy GA_{19} **69**, 15β-hydroxy GA_{44} **70** and 15β-hydroxy GA_{53} **71**. All three compounds enabled the conformation of structures for putative GAs isolated from the sunflower, *Helianthus annuus L.*.

Chater Four details the extention of previous methodolgy to produce 2β-hydroxy GA derivatives. This work lead to the confirmation of structure for three naturally occuring gibberellins 2β-hydroxy GA_{19} **82**, 2β-hydroxy GA_{44} **83** and 2β-hydroxy GA_{53} **84**, all compounds being isolated naturally from a number of different sources. Also described are some interesting issues encountered *en route*; namely the isolation of an interesting enol ether **107**, from the copper catalysed decomposition of the diazo ketone **103** , the reduction of a C-20 aldehyde in compound **89** to produce a lactone **118** under oxidative conditions and an intramolecular cannizzarro type reaction which hampered progress in the production of the 2β-hydroxy 13-deoxy derivatives.

Chapter Five details the synthesis of ten, 12-hydroxy C-20 gibberellins required for the confirmation of structures of a number of putative C-20 gibberellins. Also described is the discovery of an interesting 13-deoxygenation of a methoxymethyl protected cyclopropyl ketone **155**, during birch reduction. This deoxygenation was surprising, but allowed efficient access to the 13-deoxy derivatives.

Chapter six presents the synthesis of a new gibbrellin, *epi*-GA_{63} **195**.

Finally the future potential of the work is described in Chapter Seven.

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ABBREVIATIONS

The following abbreviations have been used throughout this thesis

Ac	Acetyl
acac	Acetylacetonate
AIBN	azobis(isobutyronitrile)
APT	Attached Proton Test
CIMS	chemical ionisation mass spectroscopy
m-CPBA	*meta*-chloroperoxybenzoic acid
DAIB	Diacetoxyiodobenzene
DEPT	Distortionless Enhancement by Polarisation Transfer
DMAP	4-(Dimethylamino)pyridine
DME	dimethoxyethane
DMF	Dimethylformamide
DQFCOSY	Double Quantum Filtered Correlation Spectroscopy
E	entgegen
EI	Electron Impact
Et	Ethyl
ether	Diethyl ether
GA	Gibberellin
HETCOR	Heteronuclear Correlation Spectroscopy
IR	Infrared
J	coupling constant
Me	Methyl
MHz	Megahertz
MOM	Methoxymethyl
mp	melting point
MPLC	Medium Pressure Liquid Chromatography
NMR	Nuclear Magnetic Resonance Spectroscopy
2D NMR	Two Dimensional Nuclear Magnetic Resonance Spectroscopy
OTf	Triflate
Ph	Phenyl
ppm	Parts per Million
TBDMS	tert-Butyldimethylsilyl
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl

Chapter One

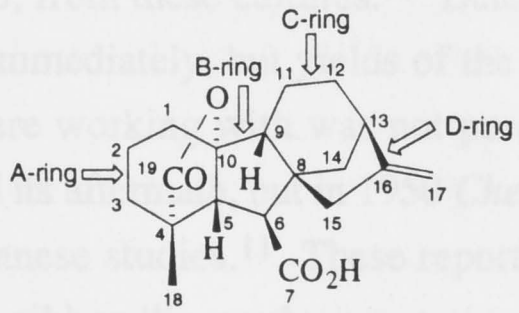
Introduction

1.1 INTRODUCTION

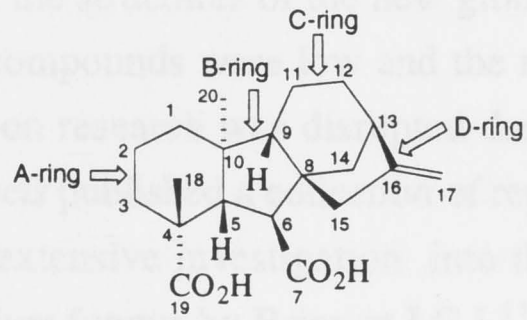
Since their isolation over fifty years ago, gibberellins have become recognised as one of the most important classes of plant bioregulators. They form a family of plant hormones that play a central role in plant growth and development. They are characterised by highly functionalised diterpenoid skeletons, with almost one hundred variations in structure.* The need to study the biology and biochemistry of gibberellins, combined with their complex structures, has made them popular targets for partial and total synthesis. These studies have uncovered a wealth of complex chemistry that has been recently reviewed.[1,2]

Gibberellins ("GAs") are widely distributed throughout the plant Kingdom with their biosynthesis being activated and inactivated during the life cycle of a plant.[3] It has been determined that gibberellins may play a role in the mechanisms of seed germination, the breaking of dormancy, enzyme synthesis, reversal of dwarfism, induction of stem growth, stimulation of flowering, modification of sex expression, parthenocarpic development of fruit, fruit enlargement and inhibition of senescence.[4] Thus, proper functioning of GA biosynthesis is essential to the normal development of higher plants.

Gibberellins can be divided essentially into two subgroups. The larger group, which is comprised of approximately two thirds of the members, contains a basic 19 carbon atom pentacyclic skeleton, for which GA_9 (gibberellin A_9 **1**) may be regarded as the parent structure. The differences within this group of compounds are accounted for mainly by the location and number of hydroxyl groups (up to four), and additional double bonds. Epoxy, oxo, or additional carboxy groups have also been observed.



GA_9 (**1**)



GA_{12} (**2**)

The remainder of the family (approximately thirty compounds) contains the full 20-carbon *ent*-gibberellane skeleton, in which the C(20) substituent ranges in oxidation level from methyl through to carboxyl. The parent compound for the C-20 GAs is

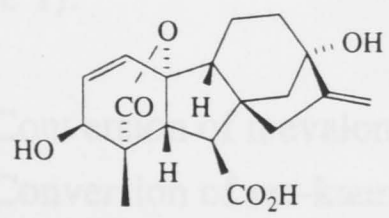
* NB: A list of naturally occurring GA's whose structures have been elucidated can be found in the Appendix.

GA_{12} **2**, with further variations in structure arising from the oxidation level of the C(20) position, in addition to the number and position of hydroxy groups (mainly 1 or 2).#

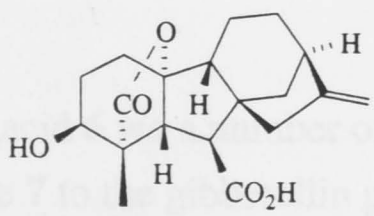
1.2 Discovery and History of Gibberellins

Gibberellin research initially began in Japan at the turn of the century, by plant pathologists working to prevent "bakanae disease" (i.e. foolish seedling). This disease resulted in the excessive elongation of rice seedlings, with the mature plant dying before reaching the stage of fruiting. At this time, "bakanae disease" was widespread throughout Japan and the Asian continent, resulting in excessive damage to rice plants, with disastrous yields of rice often being recorded (up to 40% reduction in crop yields).[6] These devastating losses motivated Japanese researchers to find the cause of this disease so that it could be prevented.

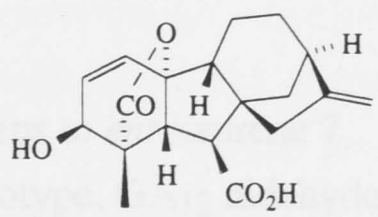
In 1898, Hori demonstrated that the phenomenon of "bakanae disease" was due to infection from a fungus, *Fusarium moniliforme*.[7] This disease could be induced in healthy plants with the microbes isolated from diseased plants. It was later found that the infection was caused by the perfect stage (sexual stage) of the fungus *Fusarium moniliforme*, called *Gibberella fujikuroi*. In 1912, Sawada published a paper that suggested that a substance produced by *Gibberella fujikuroi* was responsible for the effects of "bakanae".[8] However, firm evidence for this postulation was not obtained until 1926 by the work of Kurosawa.[9] In 1934, Yabuta isolated a crystalline compound with the same biological activity as cultures of the fungus, although it was not until 1938 that Yabuta with his associate Sumiki finally succeeded in crystallising two gibberellins, A and B, from these cultures.[10] Determination of the structures of the new gibberellins began immediately, but yields of the crystalline compounds were low and the material they were working with was not pure. Progress on research was disrupted during the war and its aftermath, but in 1950 *Chemical Abstracts* published a collection of reports on the Japanese studies.[11] These reports prompted extensive investigation into the most prolific gibberellin-producing strain of the *Fusarium* fungus by Brian at I.C.I.[11] It was found that the strain of the fungus chosen could produce mainly one gibberellin, GA_3 **3**.[12] However, by altering the conditions of the fermentation, the culture would produce a mixture of predominantly GA_4 **4** and GA_7 **5**.[13]



GA_3 (**3**)



GA_4 (**4**)



GA_7 (**5**)

NB: Once the structure of a new gibberellin has been established, it is given a code name GA_n (n = 1, 2, 3, ...), this avoids the use of trivial names.[5(a)] The nomenclature of the gibberellins in the experimental is based on the *ent*-gibberellane skeleton.[5(b)]

With the availability of reasonable quantities of GA_3, GA_4 and GA_7, the number of studies on plant responses to the application of GAs increased markedly. It was soon found that extracts from higher plants contained material that could induce biological responses identical to those elicited by the fungal gibberellins. This discovery indicated that gibberellins were present in higher plants, and led to them being isolated from these sources.[14,15]

At present, there exist close to one hundred naturally occurring GAs, with the rate of discovery continuing unabated. With greater access to GAs, many groups worldwide are seeking to understand the intricate action of this group of ubiquitous plant bioregulators. The commercial applications of gibberellins are fairly limited, due mainly to economic considerations. Nevertheless, a number of commercially viable applications are known,[16] some examples being:

(1) Reduction of time necessary for malt production in the brewing of beer.

(2) Increasing berry size in seedless grapes.

(3) Control of russet, a scab like skin disorder in apples.

(4) Uses in the flower industry for induction of flowering, either earlier or later than normal.

It is believed that, with advances in the chemical synthesis of these molecules, combined with a greater knowledge of their biology and biochemistry, vital information for the design of synthetic gibberellins or inhibitors of gibberellin metabolism will be obtained. The availability of such compounds could allow specific modification of plant growth and development which could ultimately be exploited commercially.

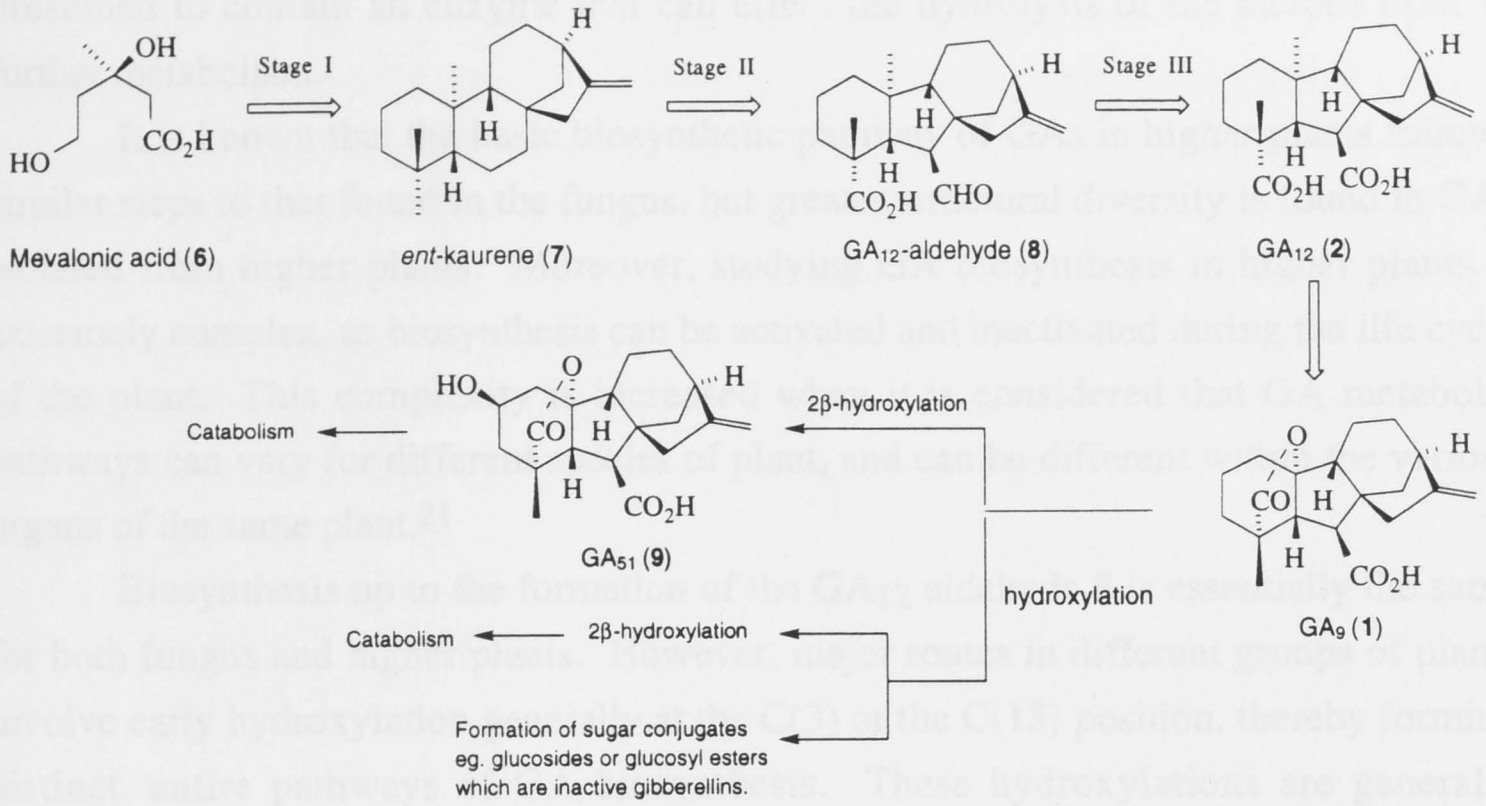
1.3 BIOSYNTHESIS OF GIBBERELLINS

The terpenoid nature of gibberellins was initially shown by Birch *et al.*[17] in 1958 by feeding studies of radio-labelled 2-^{14}C acetic acid and 2-^{14}C mevalonate to a culture of *G. fujikuroi*, resulting in the production of radiolabelled GAs. Since this initial report, a wealth of information concerning the biosynthesis of GAs has been uncovered.[3,18] It has been shown that the biosynthetic pathway to GAs in the fungus *G. fujikuroi* and in higher plants is basically the same. This pathway can be divided into three distinct stages (Scheme 1):

(1). Conversion of mevalonic acid **6** *via* a number of steps to *ent*-kaurene **7**.

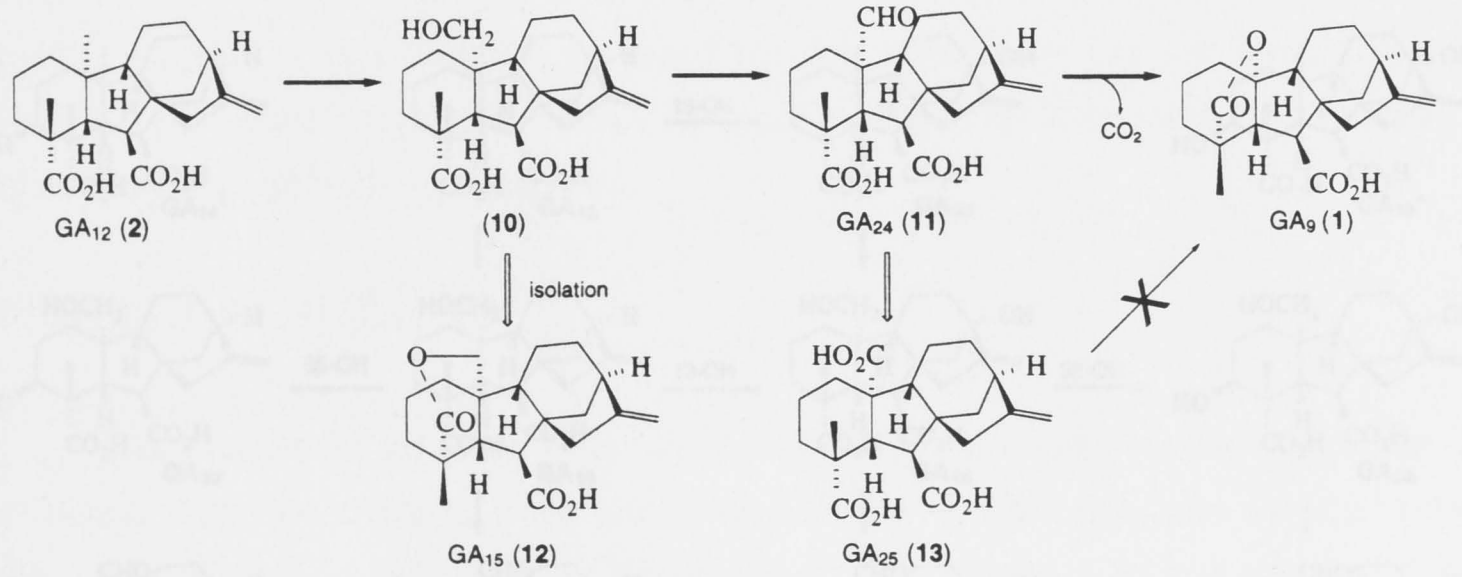
(2). Conversion of *ent*-kaurene **7** to the gibberellin prototype, GA_{12} aldehyde **8**.

(3). Conversion of GA_{12} aldehyde **8** to the C-20 GAs, thence the C-19 GAs, and finally GA inactivation either by the formation of sugar conjugates, or by 2β–hydroxylation followed by catabolism (degradation of the GA skeleton).



Scheme 1. General Biosynthetic Pathway of Gibberellins

During the third stage of biosynthesis, the conversion of the C-20 gibberellin GA_{12} **2**, to the C-19 GAs (eg. GA_9 **1**) occurs by progressive oxidation of the C(20) carbon through the sequence **2** → **10** → **11** → **1**, with the C(20) carbon ultimately being lost as carbon dioxide (Scheme 2).[19]



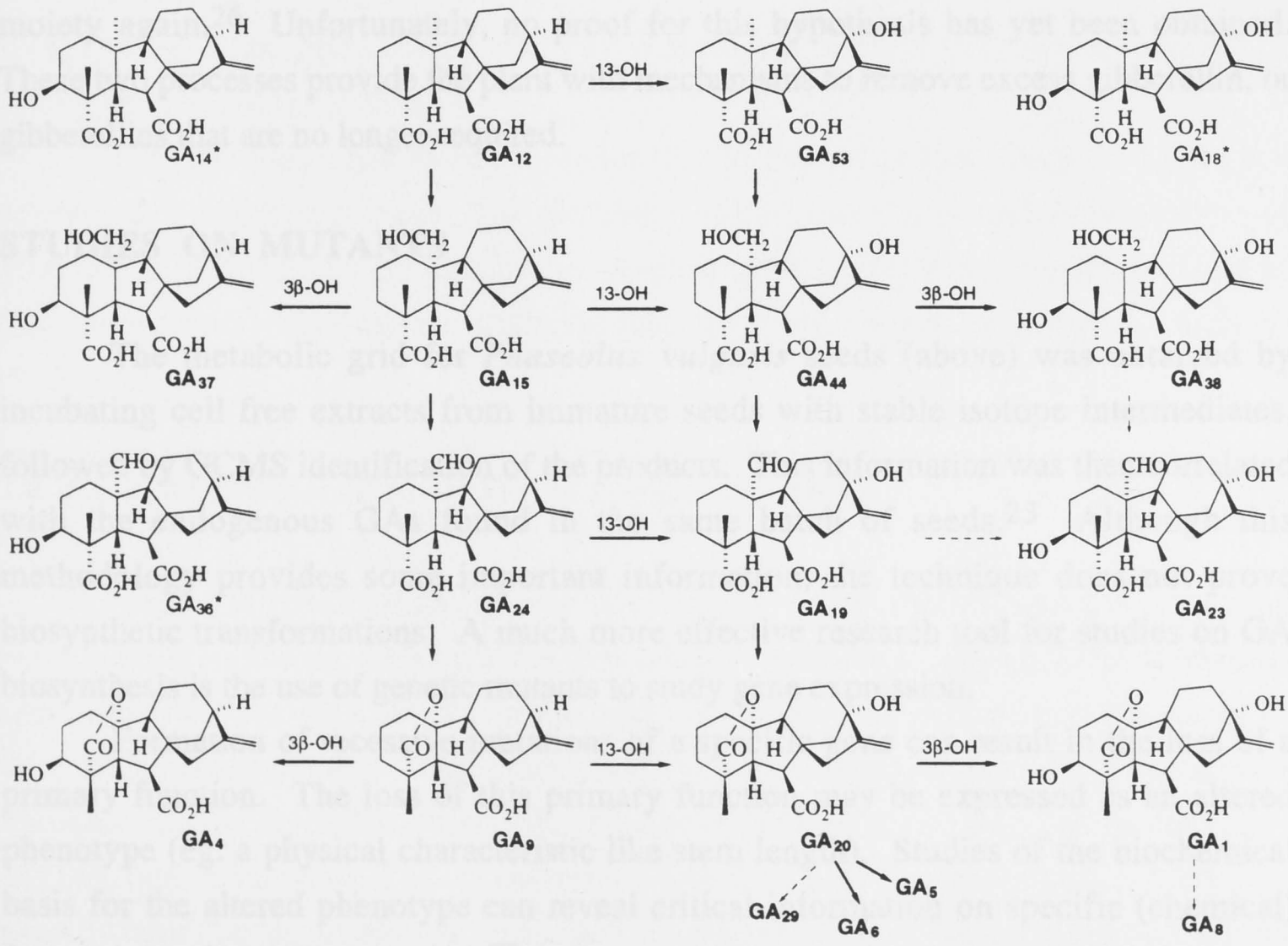
Scheme 2. Biosynthetic Pathway for the Conversion of GA_{12} to GA_9

Among the major advances in our understanding of the mechanism of GA biosynthesis are that tricarboxylic acids, such as GA_{25} **13**, are not converted to the C-19 GAs as was initially thought.[20] The tricarboxylic acids are artefacts of biosynthesis. The acids are inactive in plants and are usually disposed of through catabolism or accumulate as waste products of biosynthesis.[19] Secondly, lactones such as **12** are artefacts of isolation, in most cases isolated lactones must be hydrolysed to hydroxy acids before further oxidation can occur *in vivo*. Only a few cases are known where the lactone can be successfully oxidised *in vivo* and then further metabolised along the main GA pathway.[20] An example of hydrolysis *in vivo* is found in spinach leaves which are

presumed to contain an enzyme that can effect the hydrolysis of the lactone prior to further metabolism.

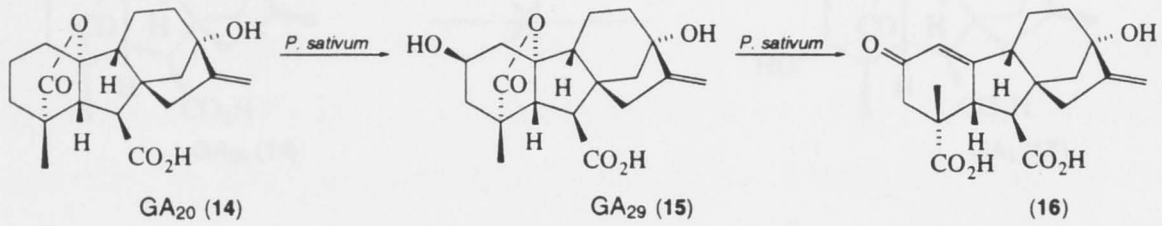
It is known that the basic biosynthetic pathway of GAs in higher plants follows similar steps to that found in the fungus, but greater structural diversity is found in GAs isolated from higher plants. Moreover, studying GA biosynthesis in higher plants is extremely complex, as biosynthesis can be activated and inactivated during the life cycle of the plant. This complexity is increased when it is considered that GA metabolic pathways can vary for different species of plant, and can be different within the various organs of the same plant.[21]

Biosynthesis up to the formation of the GA_{12} aldehyde **8** is essentially the same for both fungus and higher plants. However, major routes in different groups of plants involve early hydroxylation generally at the C(3) or the C(13) position, thereby forming distinct, entire pathways of GA biosynthesis. These hydroxylations are generally catalysed by soluble 2-oxoglutarate-dependent dioxygenases.[22] These enzymes can often be rather unspecific in their choice of substrate, thus resulting in the ability to convert a metabolite from one pathway to one from another. These interconversions lead to metabolic grids. An example of such a grid is shown for *Phaseolus vulgaris*, where both 3- and 13-hydroxylation pathways exist. In this example 3- and/or 13-hydroxylation can occur at a number of points.[23]



Partial GA biosynthetic grid from *Phaseolus vulgaris* immature seed. GAs with * are not endogenous to *Phaseolus vulgaris* . Broken lines show reactions not obtained in cell free systems.

After the loss of the C(20) carbon, thus forming the C-19 GAs, further hydroxylation of the GA skeleton can occur, as well as the introduction of olefinic linkages and other functionality's. There appear to be two mechanisms by which gibberellin activity is removed from the plant. The first is by 2β-hydroxylation, this step generally being the last in the biosynthetic sequence of gibberellins in higher plants, as it removes gibberellin activity and may precede degradation.[24] One of the many examples of this degradation pathway is found in the legume *P. sativum,* in which the conversion of GA_{20} **14** to its catabolite **16** proceeds through the 2β-hydroxy intermediate GA_{29} **15** (Scheme 3).[25]



GA_{20} (14) GA_{29} (15) (16)

Scheme 3.

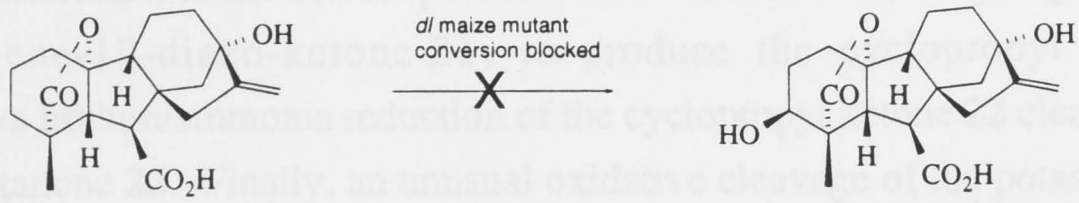
The second method by which plants may remove excess GA is by the formation of sugar conjugates such as glucosides (the sugar is linked to a hydroxy group of the GA) or glucosyl esters (sugar linked to the C(7) carboxy function) as the formation of conjugates removes GA activity.[26] It has been hypothesised that GA conjugates may be storage forms of GAs, as enzymatic hydrolysis of these conjugates should release the GA moiety again.[26] Unfortunately, no proof for this hypothesis has yet been obtained. These two processes provide the plant with mechanisms to remove excess gibberellin, or gibberellins that are no longer required.

STUDIES ON MUTANTS

The metabolic grid for *Phaseolus vulgaris* seeds (above) was obtained by incubating cell free extracts from immature seeds with stable isotope intermediates, followed by GCMS identification of the products. This information was then correlated with the endogenous GAs found in the same batch of seeds.[23] Although this methodology provides some important information, the technique does not prove biosynthetic transformations. A much more effective research tool for studies on GA biosynthesis is the use of genetic mutants to study gene expression.

Formation of recessive mutations of a specific gene can result in the loss of a primary function. The loss of this primary function may be expressed as an altered phenotype (eg. a physical characteristic like stem length). Studies of the biochemical basis for the altered phenotype can reveal critical information on specific (chemical) factors controlling the phenotype.[27]

This technique is best illustrated with the work done on dwarf mutants of maize.[27] It is known that the major pathway of GA biosynthesis in maize consists of early 13-hydroxylation, with conversion through to GA_1 **17**. It has been shown that GA_1 is the only active GA in this series, and has been directly linked to shoot elongation in maize. A number of mutants have been formed that lack the enzymes required to synthesise their own GA_1. The biosynthetic pathway in each of these mutants is blocked at specific, and different steps in the GA biosynthetic pathway. Thus, for the maize mutant *dl* it has been shown that the conversion from GA_{20} **14** to GA_1 **17** is blocked.



GA_{20} (**14**) GA_1 (**17**)

Evidence for the location of the gene block is as follows:

(1) GA_{20} has less than 1% of the activity of GA_1 when assayed on *dl* seedlings, whereas GA_{20} is as active as GA_1 for mutants blocked earlier in the sequence

(2) The level of endogenous GA_1 in *dl* seedlings is less than 2% of that present in normal seedlings

(3) Endogenous GA_{20} accumulates in the *dl* seedling to a level ten times that found in normal seedlings

(4) GA_{20} is not metabolised to GA_1 by *dl* seedlings, whereas normal seedlings do metabolise GA_{20} to GA_1.

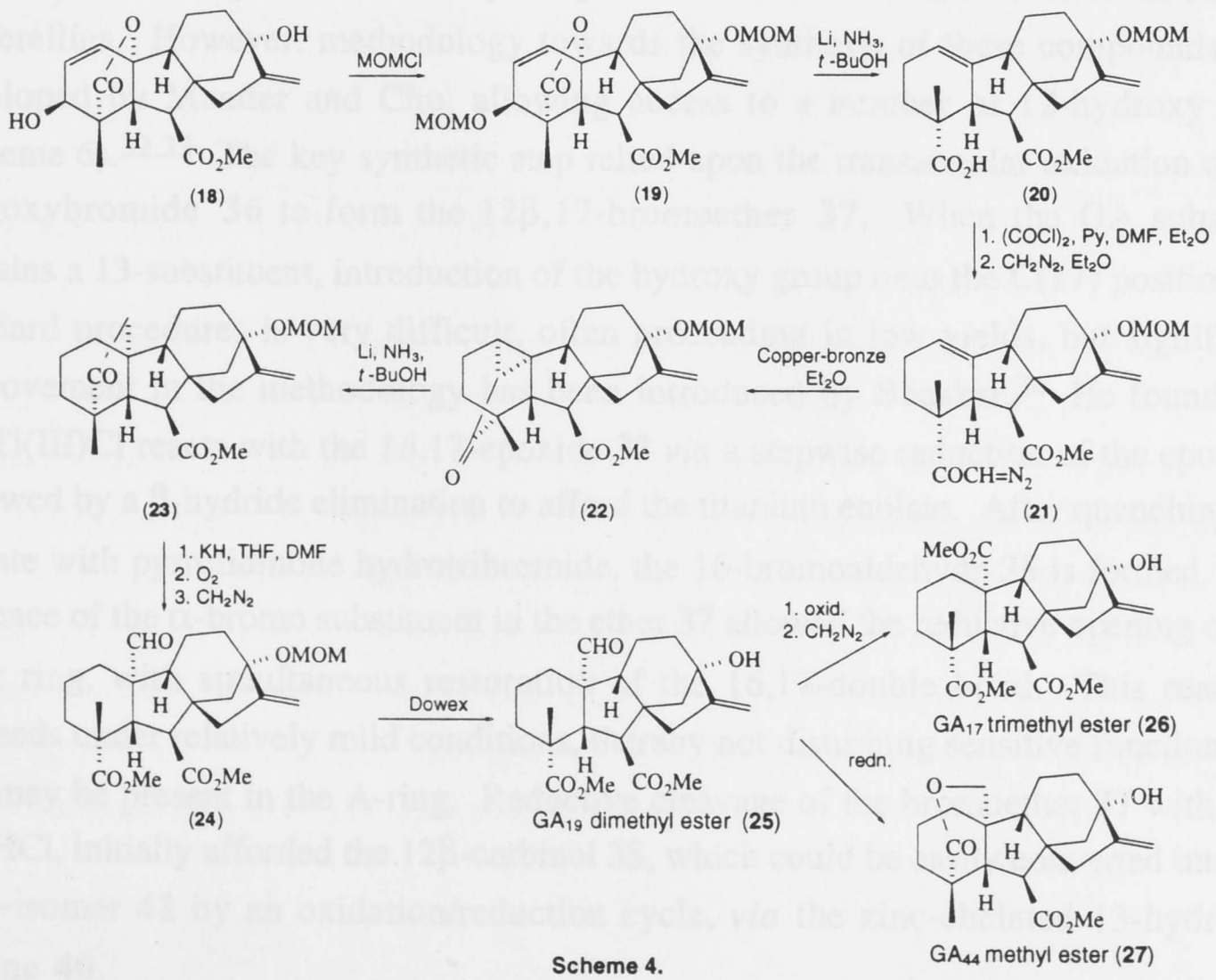
This technique has thereby proven that in normal maize, GA_{20} and GA_1 are connected in their biosynthesis. The usefulness of the genetic approach to the analysis of growth and development is clear. Much progress is being made in the understanding of the connections between biosynthesis and their effects on phenotypes (such as dwarfism).

1.4 Partial Synthesis of Gibberellins

Most gibberellins have been isolated in trace quantities, and structure identification for these compounds has depended on tentative assignments based on mass spectrometric data, as well as chromatographic behaviour. It has been necessary to confirm the assignments of these compounds by partial synthesis from the more readily available fungal GAs. Moreover, in the quest to understand the biology and biochemistry of GAs, useful amounts of many natural, as well as unnatural gibberellins, are required as substrates for metabolism studies, and for assays of their bioactivities. As useful amounts of the desired compounds are not readily accessible, either by isolation of GAs from plant tissues, or by total synthesis, partial synthesis has allowed the production of

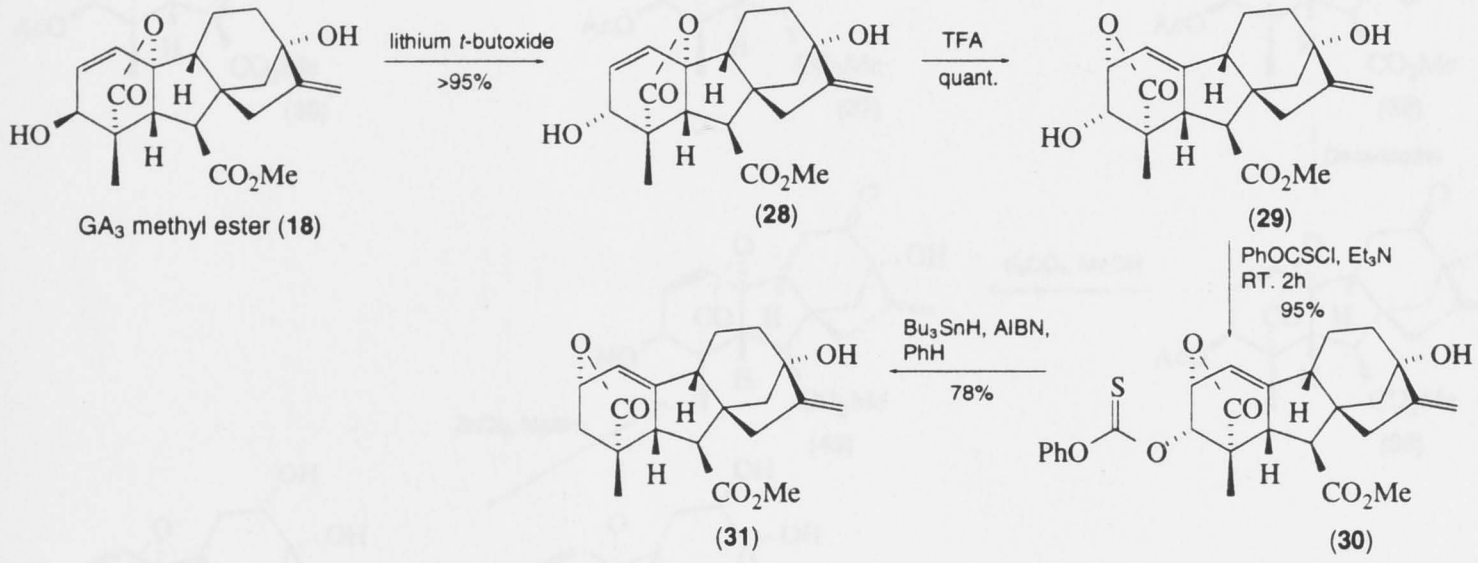
many useful and often rare GAs. In the Mander group, many advances have been made in the partial synthesis of GAs, with methodology now in place to synthesise most hydroxy and alkene derivatives of both C-19 and C-20 GAs. The chemistry of gibberellins has been comprehensively reviewed rather recently,[1,2] so only the syntheses important to this work are considered here.

One major breakthrough for gibberellin research has been the stereoselective partial synthesis of the 13-hydroxy C-20 gibberellin GA_{19} dimethyl ester **25** from freely available GA_3 **18** methyl ester (Scheme 4) by Dawe *et al.*[28] In this synthesis, the C(20) carbon is introduced into the correct position *via* an intramolecular cyclopropanation of the 1(10)-ene-19-diazo-ketone **21**, to produce the cyclopropyl ketone **22**. Regioselective lithium/ammonia reduction of the cyclopropyl ketone **22** cleanly produces the cyclopentanone **23**. Finally, an unusual oxidative cleavage of the potassium enolate of the cyclopentanone **23** by oxygen gas, followed by esterification and removal of the 13-methoxymethoxy group, affords the desired GA_{19} dimethyl ester **25**. Simple oxidation of the aldehyde in GA_{19} dimethyl ester **25**, followed by treatment with diazomethane affords easy access to the C(20) acid GA_{17} trimethyl ester **26**, while reduction of the aldehyde provides the C(20) lactone GA_{44} methyl ester **27**. However, reduction of any of these compounds to produce C(20) methyl derivatives has been an elusive goal. This methodology was later extended to the production of the 3,13-dihydroxy compounds GA_{23} and GA_{38}, as well as the production of a number of deutero and radiolabelled derivatives.[29] This methodology has thereby allowed access to many important compounds which are key intermediates in the biosynthesis of C-19 GAs.



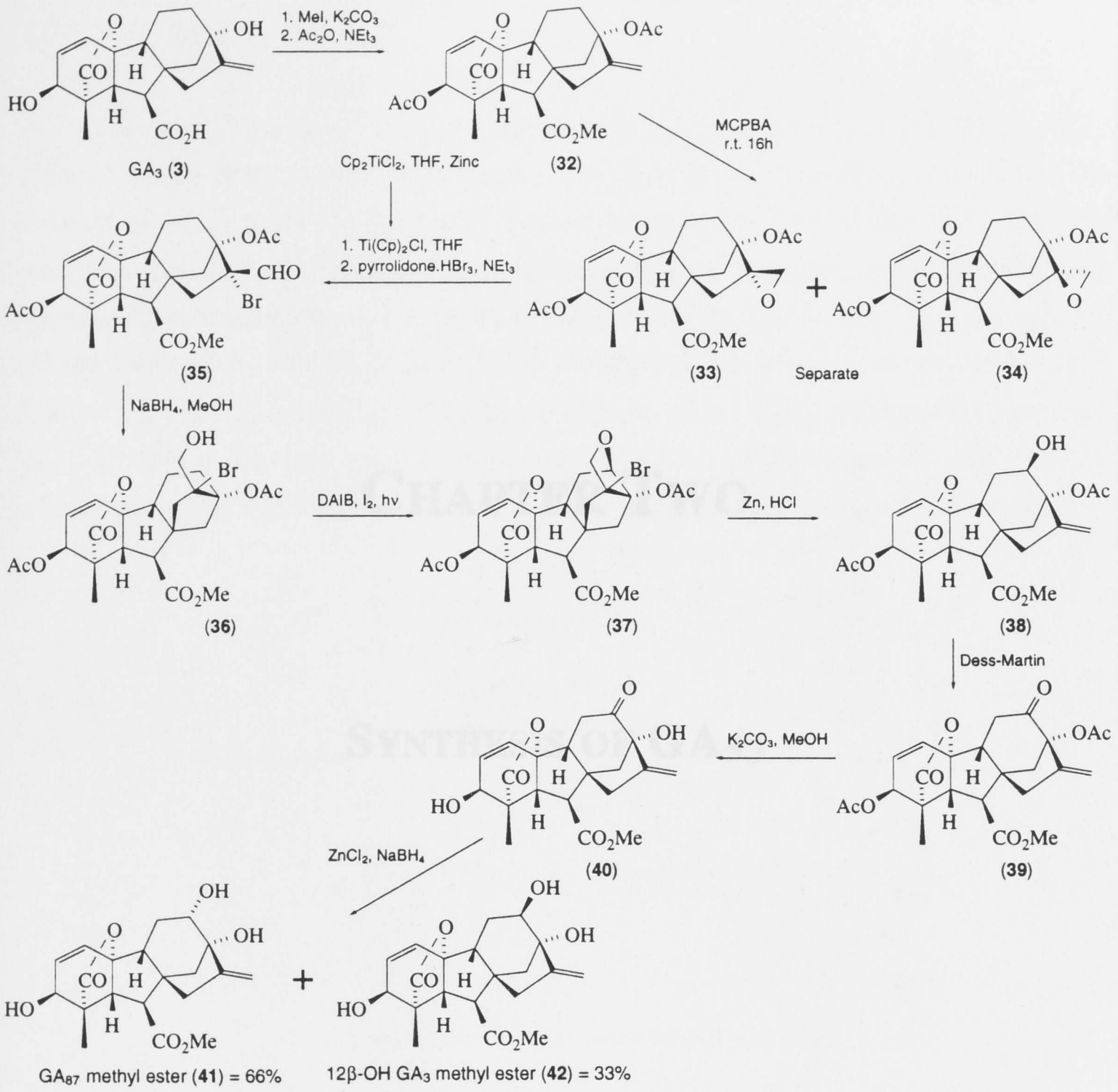
Scheme 4.

Two other important partial syntheses necessary for the work presented in this thesis were the preparation of the isolactone **31**, and secondly, the production of the 12-hydroxy GAs. The synthesis of the isolactone had been achieved previously by MacMillan *et al.*,[30] but the synthesis by Mander and Sherburn[31] represents a useful improvement. The synthetic sequence consists of four high yielding steps that can be performed relatively easily on a large scale (Scheme 5). Thus, starting with GA_3 methyl ester **18** the desired isolactone **31** was obtained in 70% overall yield. The epimerisation of the 3-hydroxy group was found to be essential. When the 3β-thiocarbonate (formed from the 3β-hydroxy group) was subjected to the conditions of the radical deoxygenation, an interesting aryl insertion of the phenyl group into the C(1) position of the GA occurred.[31]



Scheme 5.

It was thought that the 12-hydroxy GAs were the least accessible of the natural gibberellins. However, methodology towards the synthesis of these compounds was developed by Mander and Chu, allowing access to a number of 12-hydroxy GAs (Scheme 6).[32,33] The key synthetic step relied upon the transannular oxidation of the hydroxybromide **36** to form the 12β,17-bromoether **37**. When the GA substrate contains a 13-substituent, introduction of the hydroxy group onto the C(17) position *via* standard procedures is very difficult, often proceeding in low yields, but significant improvement in the methodology has been introduced by Bhaskar.[34] He found that $Cp_2Ti(III)Cl$ reacts with the 16,17-epoxide **33** *via* a stepwise reduction of the epoxide, followed by a β-hydride elimination to afford the titanium enolate. After quenching the enolate with pyrrolidinone hydrotribromide, the 16-bromoaldehyde **35** is formed. The presence of the α-bromo substituent in the ether **37** allowed the reductive opening of the ether ring, with simultaneous restoration of the 16,17-double bond. This reaction proceeds under relatively mild conditions, thereby not disturbing sensitive functionality that may be present in the A-ring. Reductive cleavage of the bromoether **37** with zinc and HCl, initially afforded the 12β-carbinol **38**, which could be easily converted into the 12α–isomer **41** by an oxidation/reduction cycle, *via* the zinc-chelated 13-hydroxy-12-one **40**.



Scheme 6. Synthesis of 12α- and 12β-Hydroxy GA_3 Methyl Ester

1.5 Aims and Goals of this Project

The initial aim of this project was to extend the methodology used in the production of C(20) GAs, to include the C(20) methyl compounds. This target has been an elusive goal for partial synthesis from gibberellins per se. However, with the methodology in place, all four oxidation levels of the C(20) position would be accessible.

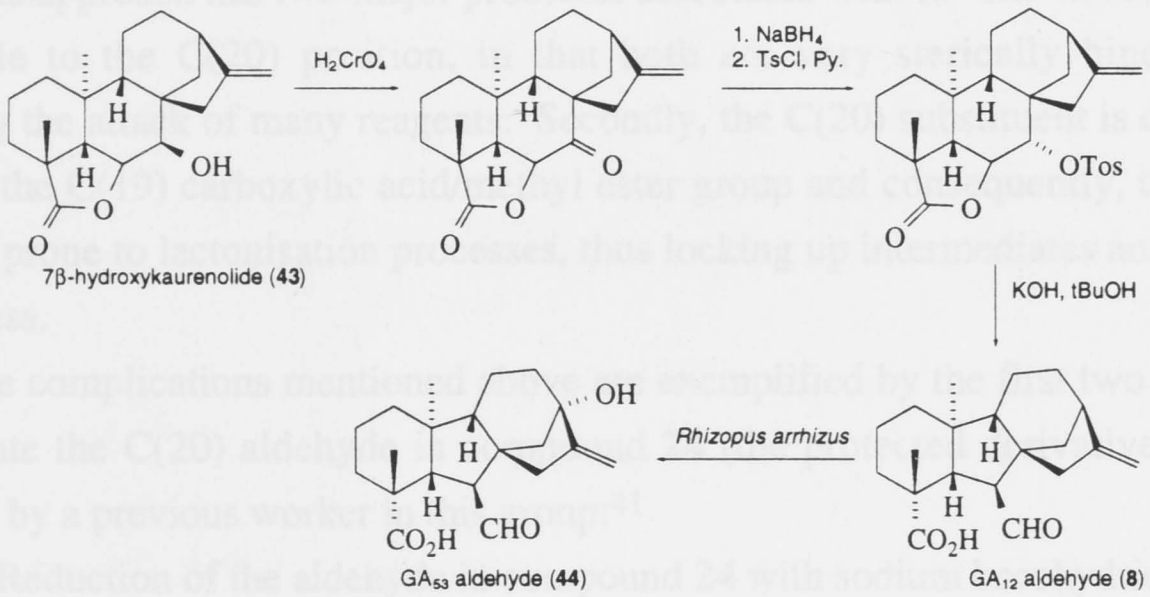
Once this goal had been successfully achieved, the next goal was to exploit the methodology elaborated above to produce a number of different hydroxylated C-20 GAs, including 2- and 12-hydroxy, as well as 2,13-, 12,13- and 13,15-dihydroxy derivatives. Many of these derivatives were thought to be putative GAs, and many were required for various biological tests and biosynthetic studies.

Chapter Two

Synthesis of GA_{53}

2.1 INTRODUCTION

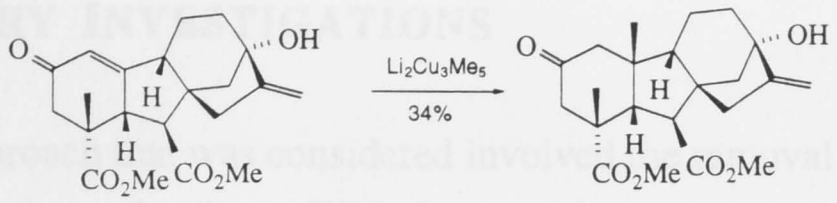
Previously, the most efficient way to obtain the 20-methyl GAs was by means of a pinacol type β-ring contraction in kaurenolide derivatives. The first example was the synthesis of GA_{12} aldehyde **8** from 7β-hydroxykaurenolide **43** (Scheme 7).[35] The 7β-hydroxykaurenolide **43** can be isolated with relative ease from the neutral fraction after fermentation and extraction of *Gibberella fujikuroi*.[36] The methodology was extended to the synthesis of GA_{14} aldehyde from 3β,7β-dihydroxykaurenolide,[37] as well as GA_{15}.[38] More recently the microbiological 13-hydroxylation of the GA_{12} aldehyde **8** to produce GA_{53} aldehyde **44**, has been achieved using *Rhizopus arrhizus* [39] (Scheme 7). Unfortunately, this method is not generally applicable and often proceeds in low yields.



Scheme 7. Conversion of Kaurenolide (43) to C(20) GAs

In order to confirm putative GA structures possessing a 20-methyl group, and to glean information on the biosynthesis of these compounds, it was necessary to develop a more general method for the production of the C-20 methyl derivatives. However, achieving this goal is not trivial, as the C(10) position of a gibberellin is particularly sterically congested. Moreover, the α-face of the gibberellin skeleton is concave, and to obtain the correct stereochemistry at C(10), reagents must attack the more sterically hindered face of the molecule.

Previous work by Beale focused on the methylation of C(10) with organocuprates.[40] In this work, conjugate addition of lithium methylcuprates to gibberell-1(10)-en-2-one dimethyl ester **45** resulted only in the production of the 2-oxo-10-*epi*-gibberellin A_{53} dimethyl ester **46**, the wrong isomer (Scheme 8). Attack on the α–face at the C(10) position was not detected, and generally, the reactions proceeded in relatively poor yields.



(45) (46)

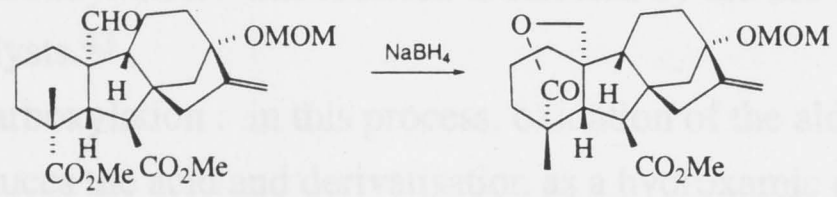
Scheme 8. Conjugate Addition of Organocuprates

It was thought that the best way towards achieving the introduction of a 20-methyl group was *via* the well-established methodology used in producing the protected derivative of GA_{19} **24** (as described in the introduction, Scheme 4, p 9).[28] This methodology introduces the C(20) carbon into the correct position with the correct stereochemistry. A number of ideas had been devised to manipulate the functionality of the C(20) aldehyde, with a view to reducing the aldehyde to the C(20) methyl compound.

This approach has two major problems associated with it. The C(10) position is comparable to the C(20) position, in that both are very sterically hindered, thus prohibiting the attack of many reagents. Secondly, the C(20) substituent is diaxial with respect to the C(19) carboxylic acid/methyl ester group and consequently, the group is extremely prone to lactonisation processes, thus locking up intermediates and rendering them useless.

The complications mentioned above are exemplified by the first two attempts to deoxygenate the C(20) aldehyde in compound **24** (the protected derivative of GA_{19}), performed by a previous worker in this group:[41]

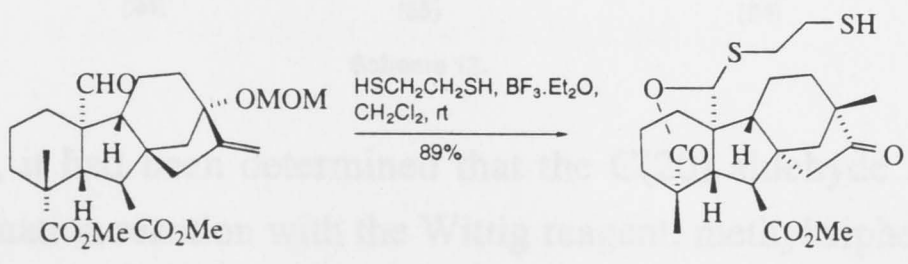
1) Reduction of the aldehyde in compound **24** with sodium borohydride produces the desired C(20) alcohol, but due to its proximity to the C(19) ester group this rapidly lactonises to furnish the protected derivative of GA_{44} **47**:



(24) (47)

Scheme 9.

2) Attempts at forming the dithiane at the C(20) aldehyde position in compound **24** as a prelude to deoxygenation were unsuccessful, as the C(19) methyl ester is fairly labile and preferentially undergoes lactonisation (the boron trifluoride etherate also causes rearrangement of the C-D ring of the GA) to produce compound **48**.

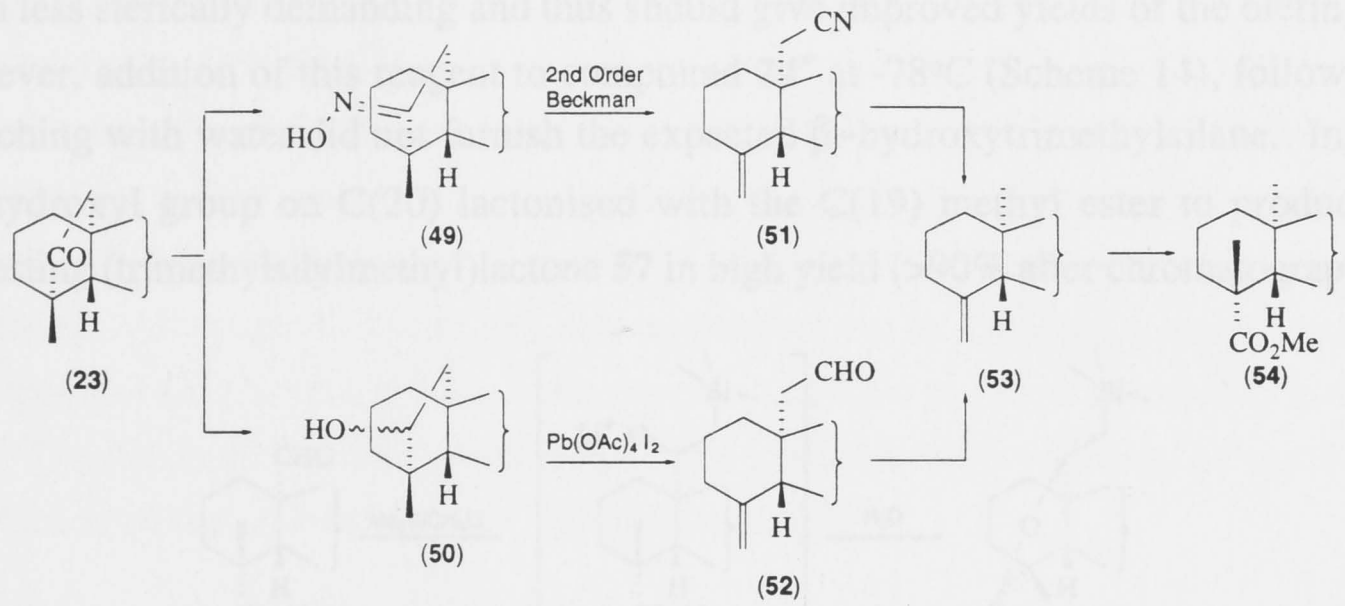


(24) (48)

Scheme 10.

2.2 PRELIMINARY INVESTIGATIONS

The first approach that was considered involved the removal of the C(19) group, after the C(20) carbon was in place. With the ester function removed, manipulation of the functionality at C(20) should be easier. Once the 20-methyl was in place, C-methylation of the reconstituted C(19) ester group was expected to yield the desired C(20) compound **54** (Scheme 11).[42] Preliminary studies of this pathway were discouraging, and were therefore not pursued.

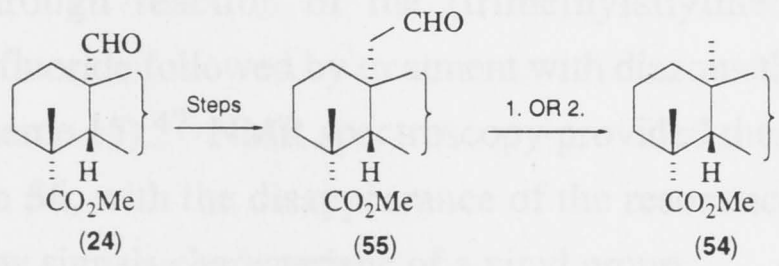


Scheme 11.

The second pathway considered, involved the homologation of the C(20) aldehyde in compound **24** (Scheme 12), followed by decarbonylation or decarboxylation of the new carbonyl group to produce protected GA_{53} **54**:

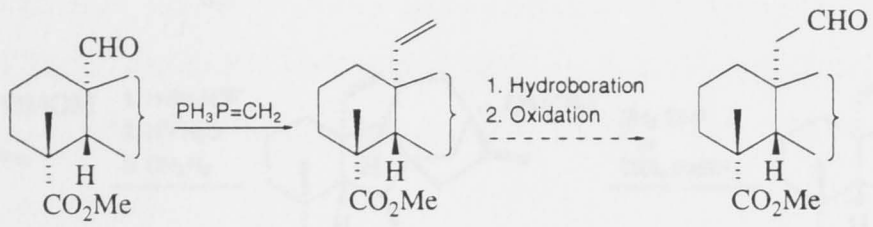
(1) Decarbonylation : this reaction is effected by the use of rhodium catalysts.[43]

(2) Decarboxylation : in this process, oxidation of the aldehyde produces the acid and derivatisation as a hydroxamic ester followed by thermolysis or photolysis, should yield the desired 20-methyl compound **54**.[44]



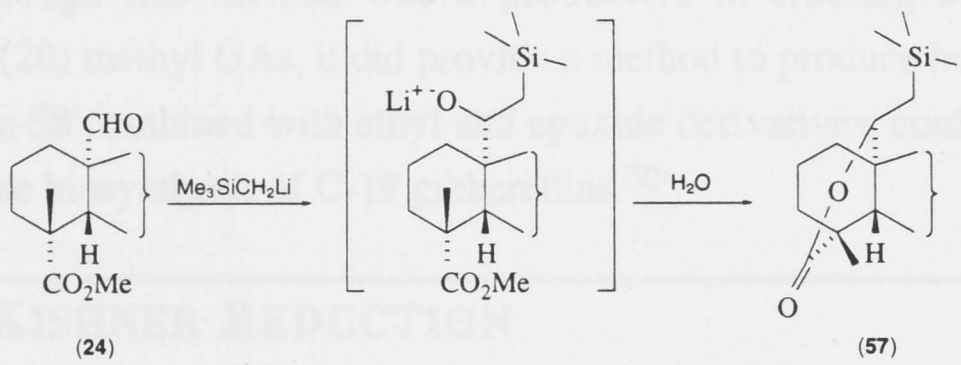
Scheme 12.

Previously, it had been determined that the C(20) aldehyde in compound **24** undergoes an olefination reaction with the Wittig reagent, methyltriphenylphosphorane, to yield the olefin **56**.[45] This olefin is a potential precursor to the homologated aldehyde **55** (Scheme 13), although the yield of the Wittig reaction is somewhat poor.[45]



Scheme 13.

The low yield of the methylenation is presumably due to the steric bulk associated with the Wittig reagent. The Peterson reagent, trimethylsilylmethyl lithium, is much less sterically demanding and thus should give improved yields of the olefin **56**.[46] However, addition of this reagent to compound **24*** at -78°C (Scheme 14), followed by quenching with water did not furnish the expected β–hydroxytrimethylsilane. Instead, the hydroxyl group on C(20) lactonised with the C(19) methyl ester to produce the interesting (trimethylsilylmethyl)lactone **57** in high yield (>90% after chromatography).



Scheme 14.

The initial evidence for the structure of compound **57** was given by mass spectrometry which showed a molecular ion of m/z 490. The ^1H NMR spectrum indicated the lactone-TMS group with a broad singlet at 4.45 ppm from H(20), combined with resonances at 0.13 ppm from the TMS group. Further evidence was obtained by ^{13}C NMR with the appearance of a resonance at -1.0 ppm for the 3 methyl groups of the TMS function, plus the extra methylene group [C(21)] at 27.8 ppm, and the absence of a methoxy signal.

This problem of lactonisation was quickly resolved and the desired olefin **56** cleanly obtained through reaction of the (trimethylsilylmethyl)lactone **57** with tetrabutylammonium fluoride followed by treatment with diazomethane (>85% yield after chromatography, Scheme 15).[47] NMR spectroscopy provided the main evidence for the structure of the olefin **56**, with the disappearance of the resonances for the TMS group combined with the new signals characteristic of a vinyl group.

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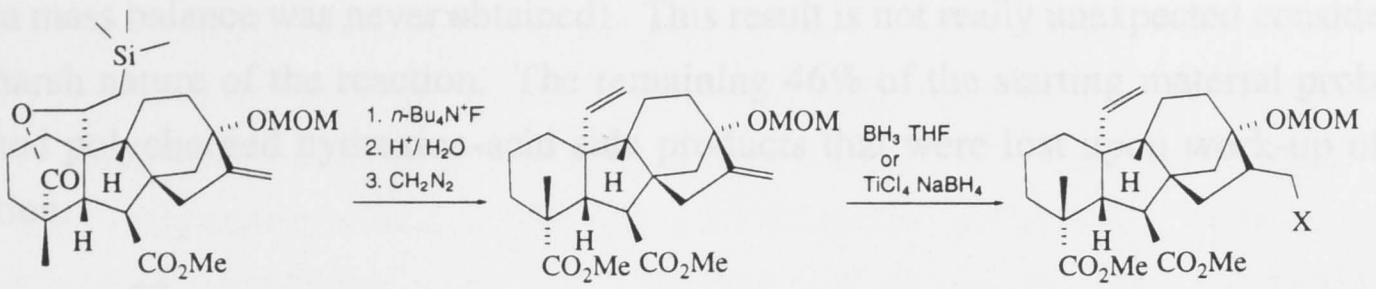
* This compound was made according to the procedure of Dawe *et al.* [28]



(57) **(56)** **(58)** X = OH OR H

Scheme 15.

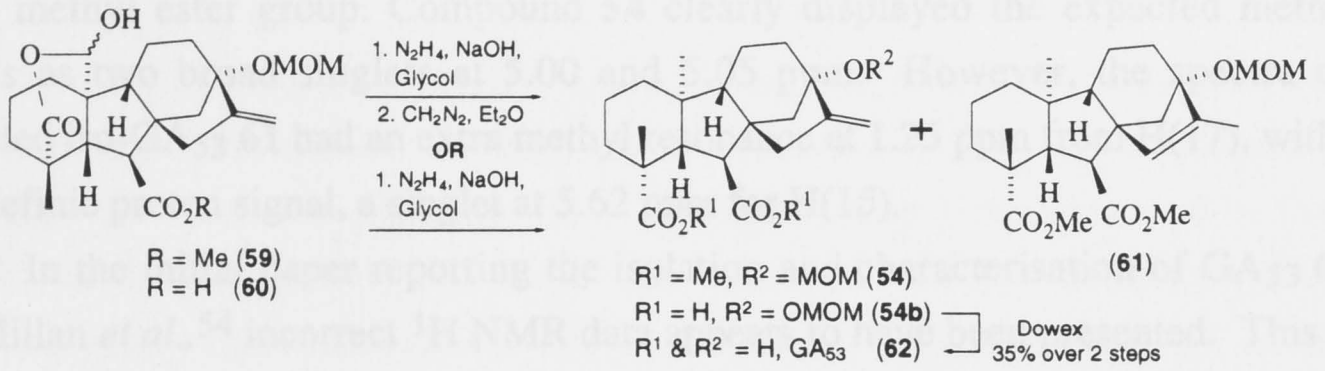
Unfortunately, hydroboration of the olefin **56** failed. Forcing conditions [up to a tenfold excess of borane reagents (borane in tetrahydrofuran[48] or titanium tetrachloride plus sodium borohydride[49]) resulted in transformation of the C(16)-C(17) olefinic bond or decomposition of the material, but did not affect the new vinylic bond (Scheme 15). The inability of the boron reagent to attack the C(20) olefin seemed to indicate that this group was hidden inside the concave face of the gibberellin, and was thus too sterically hindered. Although this method was unproductive in creating a solution to the production of C(20) methyl GAs, it did provide a method to produce homologated C-20 GAs. The olefin **58** combined with ethyl and epoxide derivatives, could be useful tools in the study of the biosynthesis of C-19 gibberellins.[50]

2.3 WOLFF-KISHNER REDUCTION

Due to the unforseen complexities in the homologation of the aldehyde **24** above, investigation of another route, using Wolff-Kishner methodology, was considered. Attempts at Wolff-Kishner reduction of the protected aldehyde **59** using the standard conditions of the Huang-Minlon procedure[51] were unsuccessful. However, it is known that this procedure is not effective for reduction of sterically hindered carbonyl groups. A report by Barton *et al.*[52] indicated that here, anhydrous conditions, using hydrazine instead of the hydrate, are necessary to effect the desired reduction. The authors state that the absence of water improves the reducing power of the reagents remarkably. Following a similar procedure, reported by Ireland *et al.*[53] (using sodium hydroxide pellets instead of the Barton procedure, which uses sodium metal) on the monomethyl ester **59**, followed by treatment of the crude reaction mixture with diazomethane, indeed furnished the protected derivative of GA_{53} **54**, mixed with the isomeric compound **61** (Scheme 16).

The initial yield of this reaction was a rather poor 27% overall yield, with the ratio of compounds **54** to **61** being 3 : 2. Optimisation of the reaction initially began with the use of the diacid aldehyde **60** instead of the methyl ester. After a number of experiments trialing different solvents, bases and reaction temperatures (see Table 1), the yield of the reaction was increased to 54% with the ratios of the isomers **54** and **61** being >5.5:1 (entry 8 in Table 1). Recovery of the remainder of the gibberellin was never achieved

(i.e. a mass balance was never obtained). This result is not really unexpected considering the harsh nature of the reaction. The remaining 46% of the starting material probably formed polycharged hydrazine-acid side products that were lost upon work-up of the reaction.



Scheme 16.

Table 1: Wolff-Kishner Reductions Optimisation Results

Starting material	solvent	hydroxide base	final heating temp.	isolated yield %†	nmr ratio exo:endo (54):(61)
1. 7-ester (**59**)	Digol	NaOH	175 ± 4 °C	27%	3 : 2
2. diacid (**60**)	Digol	NaOH	170 ± 4 °C	45%	5 : 1
3. diacid (**60**)	Digol	NaOH	174 ± 4 °C	59%	3 : 2
4. diacid (**60**)	Methyl digol	NaOH	172 ± 4 °C	67%	2.5 : 1
5. diacid (**60**)	Methyl digol	KOH	170 ± 4 °C	42%	6 : 1
6. diacid (**60**)	Methyl digol	LiOH	170 ± 4 °C	28%	3 : 1
7. diacid (**60**)	Propane-1,2-diol	NaOH	172 ± 4 °C	21%	not determined
8. diacid (**60**)	Ethanediol	NaOH	174 ± 4 °C	54%	5.5 : 1

† The yields displayed here are the combined yields of both isomers, as compound **54** and **61** could only be separated by careful MPLC chromatography.

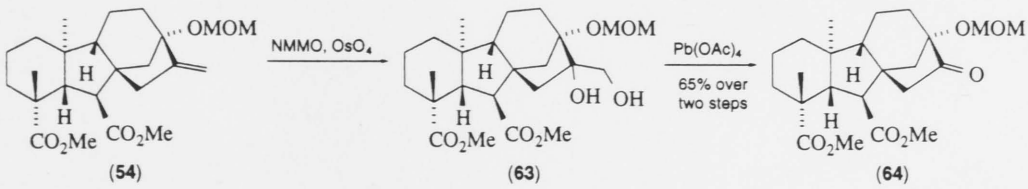
The hydrolysis of the methyl ester groups of the protected GA_{53} **54** derivative was very difficult, as will be discussed in the next section. Thus, treatment of the crude reaction mixture **54(b)** with Dowex resin (rather than with diazomethane) produced the fully deprotected material **62** (Scheme 16). Purification of the material on silica gel, followed by crystallisation, afforded the desired GA_{53} **62** in 35% overall yield from the diacid aldehyde **60**.

Spectroscopic proof for the assignment of the structures for **54** and **61** was mainly obtained by ^{1}H NMR spectroscopy. In both compounds **54** and **61**, the C(20) methyl group gave rise to an upfield resonance of 0.69 and 0.65 ppm respectively. This high field resonance is characteristic of the C(20) methyl group being shielded by the C(19) methyl ester group. Compound **54** clearly displayed the expected methylene signals as two broad singlets at 5.00 and 5.05 ppm. However, the spectra of the protected iso-GA_{53} **61** had an extra methyl resonance at 1.25 ppm from H(17), with only one olefinic proton signal, a singlet at 5.62 ppm for H(15).

In the initial paper reporting the isolation and characterisation of GA_{53} **62**, by MacMillan *et al.*,[54] incorrect ^{1}H NMR data appears to have been presented. This paper states that the ^{1}H NMR data for the isolated sample of GA_{53} **62** were similar to that of GA_{12} **2**. However, this is clearly not the case, with all signals reported being significantly different to the expected shifts, especially, the signal for the C(20) methyl group which was reported as appearing at 1.62 ppm, whereas, in both GA_{12} **2** and the synthetic sample of GA_{53} **62** (Scheme 16) the signal appears in the range 0.8 - 0.9 ppm [due to the shielding from C(19) acid functionality].

2.4 DEUTERO DERIVATIVES

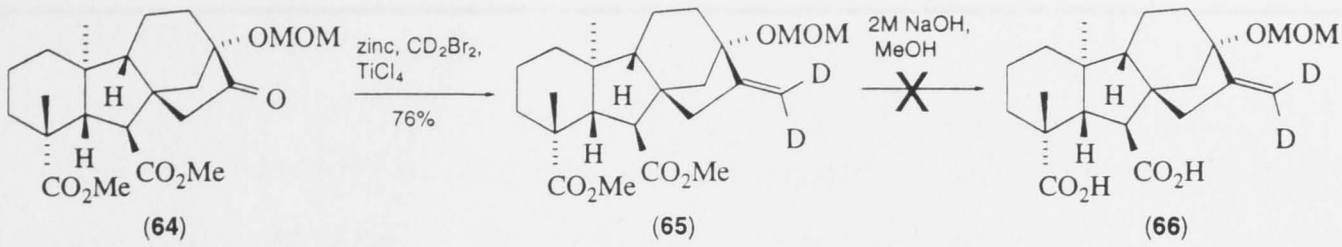
With a general method now in place to synthesise GA_{53} **61**, deutero derivatives were now prepared for the quantification of gibberellins from feeding studies.[55] Synthesis of the desired d_2-GA_{53} **68** could be achieved with relative ease using standard methodology for routinely producing material labelled at the olefinic C(17) position.[56] Dihydroxylation of GA_{53} dimethyl ester **54** with osmium tetroxide, followed by cleavage of the resulting diol **63** with lead tetraacetate proceeded smoothly, producing compound **64** in 65% overall yield (Scheme 17).



(54) (63) (64)

Scheme 17.

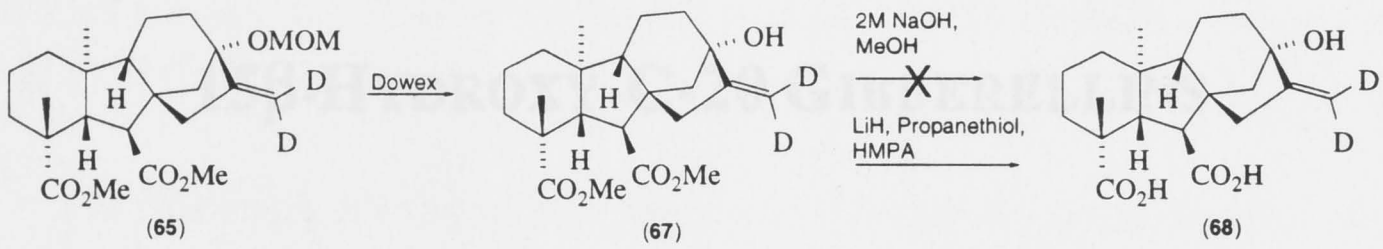
The 16-norketone **64** was then treated with labelled Lombardo reagent (Scheme 18).[56] This was formed from dideuterodibromomethane, zinc and titanium tetrachloride and reacted smoothly with the norketone to produce the desired dideutero GA_{53} dimethyl ester **65** in 76% yield. Both ^{1}H and ^{13}C NMR spectra of the deutero compound **65** corresponded precisely with the nondeuterated sample **54**, except for the H(17) and C(17) resonances, which were not observed.



(64) (65) (66)

Scheme 18.

Hydrolysis of the methyl esters under forcing conditions failed, with only starting material being obtained after heating under reflux for 40 hours in aqueous sodium hydroxide and methanol (Scheme 18). This result may have been due to the low solubility of the protected material in the aqueous solution and so the methoxymethoxy protecting group was removed to produce compound **67** (Scheme 19). An attempt to deprotect the methyl ester groups from the hydroxy compound **67** under the standard aqueous conditions was also unsuccessful. However, the methyl esters were eventually removed by treatment with propanethiol, HMPA and lithium hydride, thereby affording the desired d_2-GA_{53} **68.**#



(65) (67) (68)

Scheme 19.

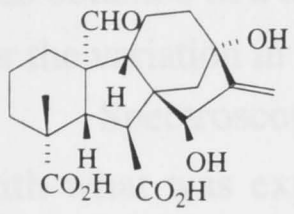
The demethylation of the ester functionality in compound **67** to produce d_2-GA_{53} **68**, by Mr B. Twitchin is greatly appreciated.

Chapter Three

15β-Hydroxy C-20 Gibberellins

3.1 INTRODUCTION

In 1988, MacMillan and coworkers isolated a number of 15β-hydroxy-gibberellins from the seed of the sunflower *Helianthus annuus L.*[57] Four of these gibberellins were tentatively assigned as the structures 15β-hydroxy-GA_{19} **69**, 15β-hydroxy GA_{44} **70,** 15β-hydroxy GA_{53} **71** and 15β-hydroxy GA_{17} **72**. Synthetic samples of these compounds were required in order to confirm their identities. The synthesis of all of these compounds was straightforward, based on the work carried out by MacMillan *et al.* in their synthesis of GA_{63} **196** (Chapter 6, p 66).[58]



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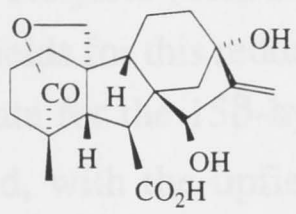

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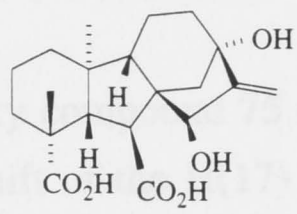
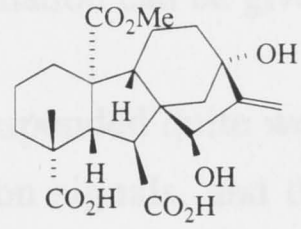


(71)

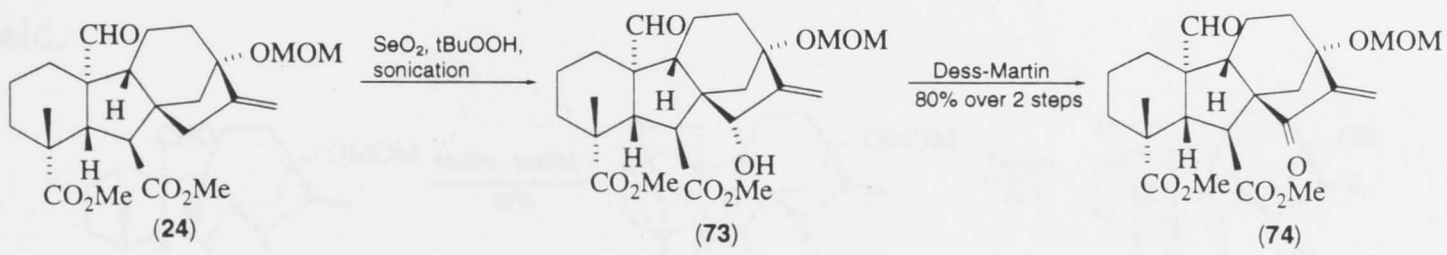


(72)

3.2 SYNTHESIS OF 15β-HYDROXY GA_{19}, 15β-HYDROXY GA_{44} AND 15β-HYDROXY GA_{53}

The first target of this synthetic study was 15β-hydroxy GA_{19} dimethyl ester **76** (Scheme 21). The other two target compounds, 15β-hydroxy GA_{44} methyl ester **78** (Scheme 22) and 15β-hydroxy GA_{53} dimethyl ester **81** (Scheme 23), should then be obtainable from compound **75** (Scheme 21). The synthetic sequence to produce compound **76** would start with GA_{19} dimethyl ester **24**, and would follow the steps used in the synthesis of GA_{63} **196** as reported by MacMillan.[58]

Allylic oxidation of GA_{19} dimethyl ester **24** with selenium dioxide and *t*-butylhydroperoxide under sonication afforded the 15α-hydroxy derivative **73** (Scheme 20).[59] Due to the fact that the 15α-hydroxy group is prone to lactonize with the 7-methyl ester, the material was used without purification and oxidised to the enone **74** using the Dess-Martin reagent.[60]



(24) (73) (74)

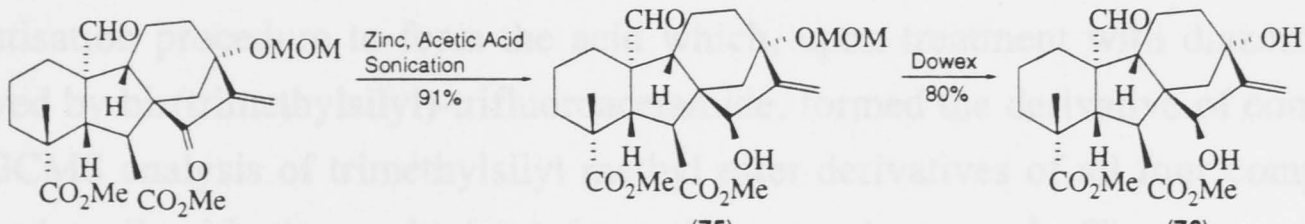
Scheme 20.

In MacMillan's synthesis of GA_{63} **196**, Swern oxidation[61] was used to produce the desired enone. However, in the Mander group the Dess-Martin reagent[60] has been found to be a superior reagent for simple oxidation of primary and secondary alcohols. Thus, the enone **74** was isolated cleanly in 80% yield over the two steps

Characteristic ^{1}H NMR resonances for the C(17) olefinic protons at 5.45 and 6.08 ppm, combined with the appearance of the carbonyl resonance at 205.1 ppm in the ^{13}C NMR spectrum, confirmed the assignment of the structure of the enone **74**.

For the reduction of GA-15-ones to allylic alcohols, the use of zinc and acetic acid has been shown to be superior to the hydride/lanthanide reagents more commonly employed for this transformation.[58] Generally, the yield for this reducing system deteriorates when applied to C-19 GAs containing 13-oxygen substituents, often dropping below 30% for polyhydroxylated GAs.[58,62] Thus, it came as a pleasant surprise that upon reduction of the enone **74**, the desired 15β-hydroxy compound **75** was obtained in a high 91% yield (Scheme 21). No reasonable explanation can be given for the variation in the yields for this reduction.

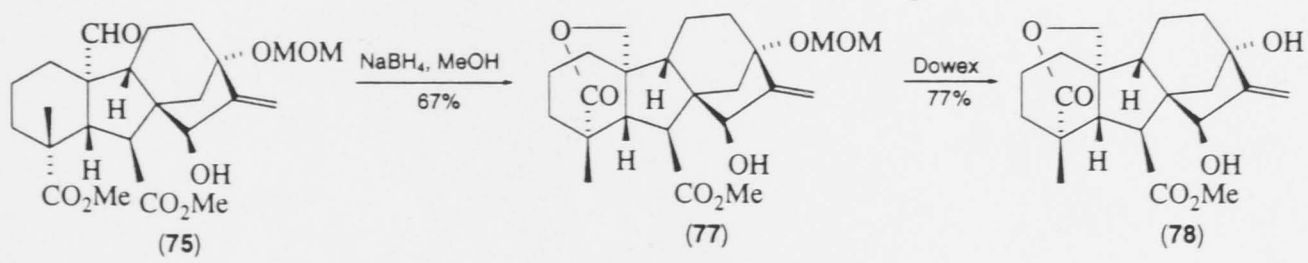
Spectroscopic data for the 15β-hydroxy compound **75** corresponded quite well with what was expected, with the upfield shift of the H(17) proton signals, and the 15α-proton appearing as a broad singlet at 4.07 ppm in the ^{1}H NMR spectrum. Finally, treatment of the protected aldehyde **75** with Dowex resin in methanol under reflux efficiently removed the methoxymethoxy protecting group in 80% yield (Scheme 21).[63] Thus, desired 15β-hydroxy GA_{19} dimethyl ester **76** was obtained in 58% overall yield from the starting aldehyde **24**.



(74) (75) (76)

Scheme 21.

Reduction of the protected aldehyde **75** with sodium borohydride in methanol at 0°C cleanly afforded the desired protected 15β-hydroxy GA_{44} derivative **77** in 67% yield (Scheme 22). Removal of the methoxymethoxy protecting group was achieved by treatment of the protected lactone **77** with Dowex resin in methanol under reflux.[63] This reaction supplied the deprotected material, 15β-hydroxy GA_{44} methyl ester **78**, in 77% yield.

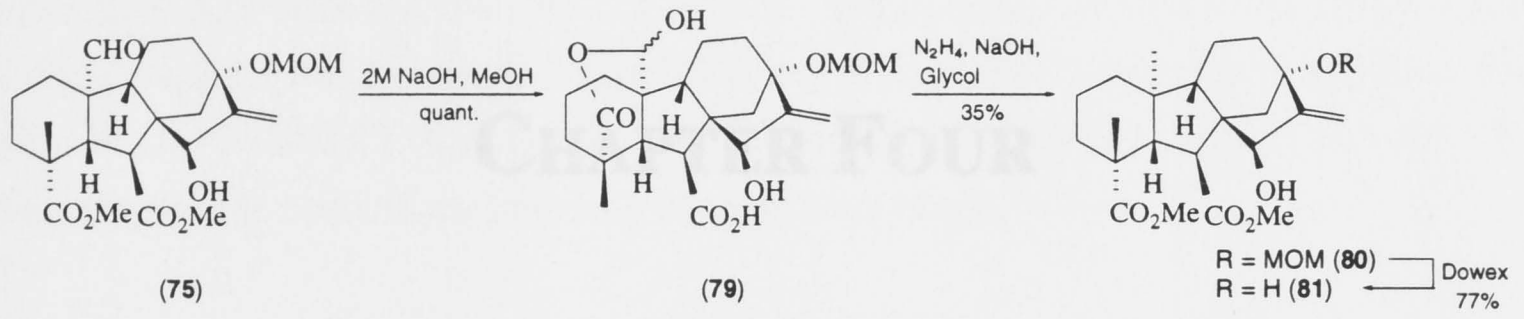


(75) (77) (78)

Scheme 22.

The synthesis of the dimethyl ester of 15β-hydroxy GA_{53} **81** followed the conditions optimised for the synthesis of protected GA_{53} **54**, found on p 18, Chapter 2. Hydrolysis of the methyl esters produced the hydroxy lactone **79** quantitatively

(Scheme 23). Wolff-Kishner reduction of this compound, followed by treatment of the crude residue with diazomethane, then purification on silica gel afforded the protected 15β-hydroxy GA_{53} **80** in 35% yield. The identity of the compound was apparent from the ^1H NMR spectrum with characteristic resonances of the 15α-proton at 4.02 ppm, and the H(20) methyl group at 0.69 ppm. Finally, treatment of compound **80** with Dowex resin in methanol under reflux yielded the desired 15β-hydroxy GA_{53} dimethyl ester **81** in 67% yield (Scheme 23).[63]



Scheme 23.

The synthesis of the trimethyl ester of 15β-hydroxy-GA_{17} **72** (Chap 3 p 22) was not attempted. However, upon GCMS analysis of the trimethylsilyl derivatives of the 15β-hydroxy GA_{19} dimethyl ester **76**, a substantial amount of an impurity characteristic of the (trimethylsilyl) methyl ester derivative of 15β-hydroxy GA_{17} **72** was found. This seemed to indicate that some of the aldehyde **76** had auto-oxidised over time or in the derivatisation procedure to form the acid which, upon treatment with diazomethane followed by bis(trimethylsilyl)-trifluoroacetamide, formed the derivative of compound **72**. GCMS analysis of trimethylsilyl methyl ester derivatives of all four compounds matched well with those obtained from the natural source.* Therefore, all four compounds are naturally occurring gibberellins and are presently being assigned GA numbers.

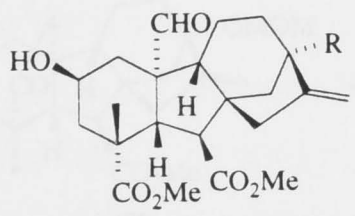
* The author gratefully acknowledges the formation of the TMS derivatives followed by GCMS analysis, for the three compounds **76**, **78** and **81** by Dr. Paul Gaskin.

CHAPTER FOUR

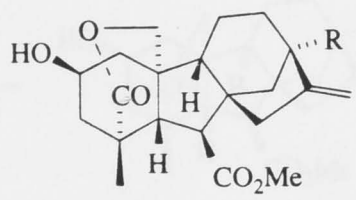
2β-HYDROXY C-20 GIBBERELLINS

4.1 INTRODUCTION

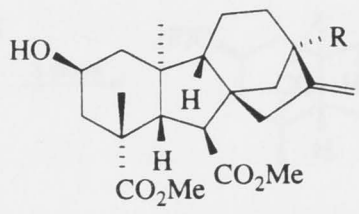
As noted in the introduction, 2β-hydroxylation is generally the last step in the biosynthetic sequence of gibberellins in higher plants.[24] It is known that C-20 gibberellins containing 2β-hydroxy substituents are rare. However, in the past couple of years a number of putative C-20 gibberellins thought to possess 2β-hydroxy substituents have been isolated from a number of different sources. Thus, authentic samples of 2β-hydroxy GA_{19} dimethyl ester **82**, 2β-hydroxy GA_{44} methyl ester **83** and 2β-hydroxy GA_{53} dimethyl ester **84**, as well as the 13-deoxy derivatives 2β-hydroxy GA_{24} dimethyl ester **85**, 2β-hydroxy GA_{15} methyl ester **86** and 2β-hydroxy GA_{12} dimethyl ester **87**, were required to confirm the identities of these compounds.



R = OH (**82**)
R = H (**85**)

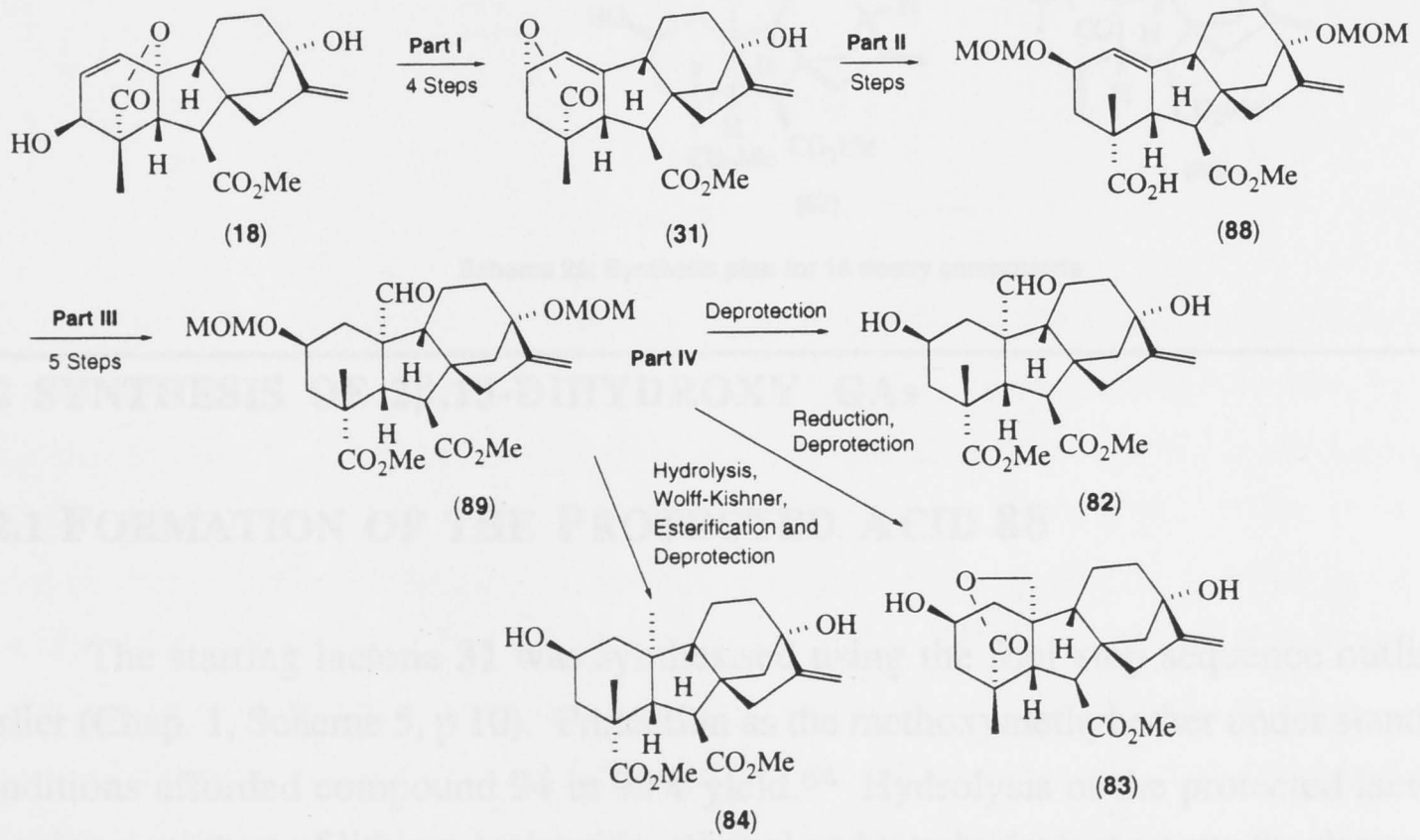


R = OH (**83**)
R = H (**86**)



R = OH (**84**)
R = H (**87**)

The synthesis of the 2β,13-dihydroxy compounds was attempted first. The synthetic plan to produce the desired compounds could be divided into four main stages (Scheme 24).

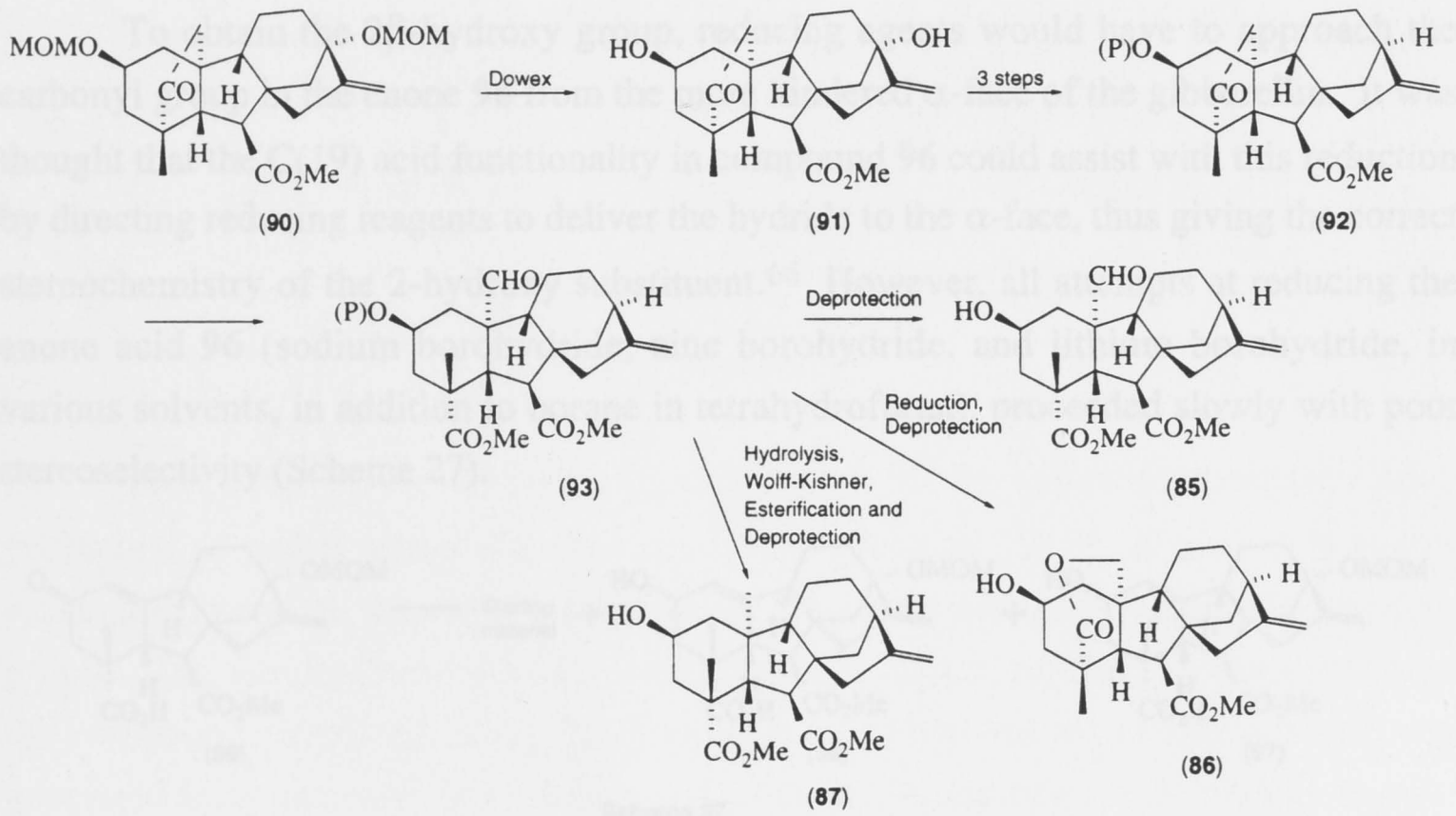


Scheme 24. Synthetic Plan for the production of 2β-OH C-20 GAs

The first of these stages constitutes the production of the lactone **31** *via* a four step procedure, the methodology for which had been previously determined within the group (explained in Chap 1, p 10). The second part of the synthesis involved opening

the lactone, inverting the stereochemistry of the 2-hydroxy group, followed by protection to produce the acid **88**. The third part of the synthesis used the acid functionality in compound **88** to build in the C(20) aldehyde using the standard five step procedure found in the synthesis of the protected GA_{19} **24** (Scheme 4, p 9). Finally, the target compounds **82**, **83** and **84** would be formed using the standard methods discussed in Chapters 2 and 3.

With the successful completion of the dihydroxy derivatives, it was then hoped that the 13-deoxy samples could be formed (Scheme 25) by deoxygenation of an advanced intermediate (eg **90**). This intermediate would then be transformed into the desired 13-deoxy compounds **85**, **86** and **87** by using similar steps to those shown above.

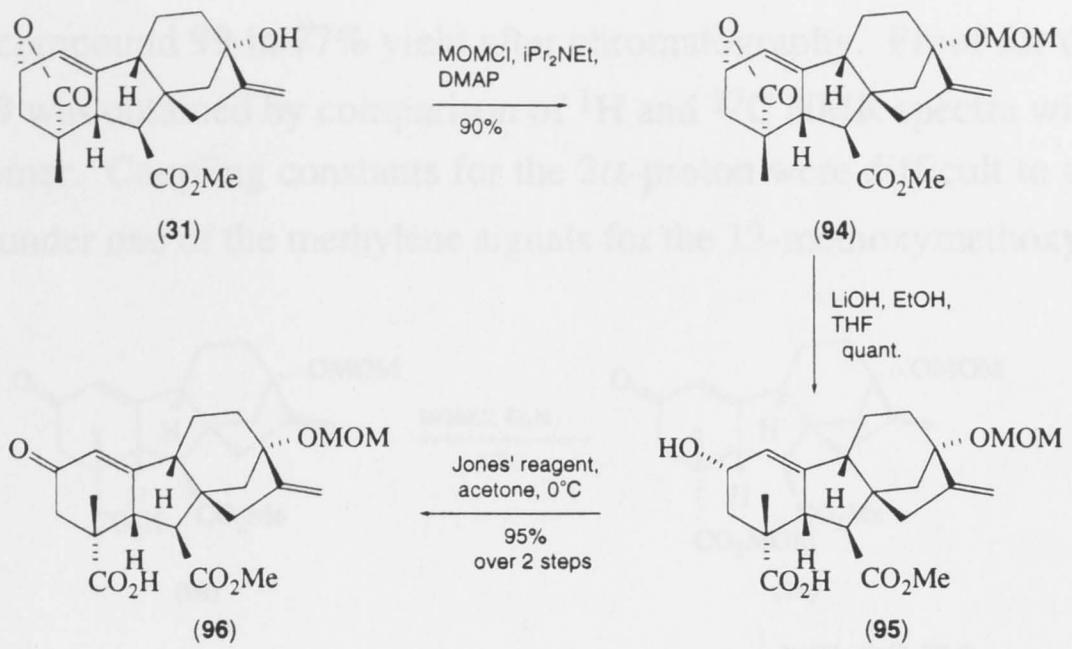


Scheme 25: Synthetic plan for 13 deoxy compounds

4.2 SYNTHESIS OF 2β,13-DIHYDROXY GAs

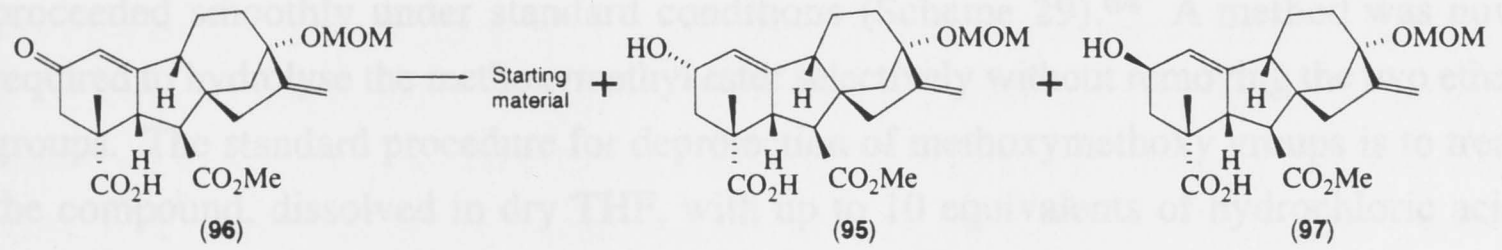
4.2.1 FORMATION OF THE PROTECTED ACID 88

The starting lactone **31** was synthesised using the four step sequence outlined earlier (Chap. 1, Scheme 5, p 10). Protection as the methoxymethyl ether under standard conditions afforded compound **94** in 90% yield.[64] Hydrolysis of the protected lactone **94** using a mixture of lithium hydroxide, ethanol and tetrahydrofuran gave the desired γ-hydroxy acid **95** in virtually quantitative yield (Scheme 26). To circumvent relactonisation, the crude material was oxidised immediately to the enone acid **96**. It was found that the best results for this transformation were obtained by using Jones' reagent.[65]



Scheme 26.

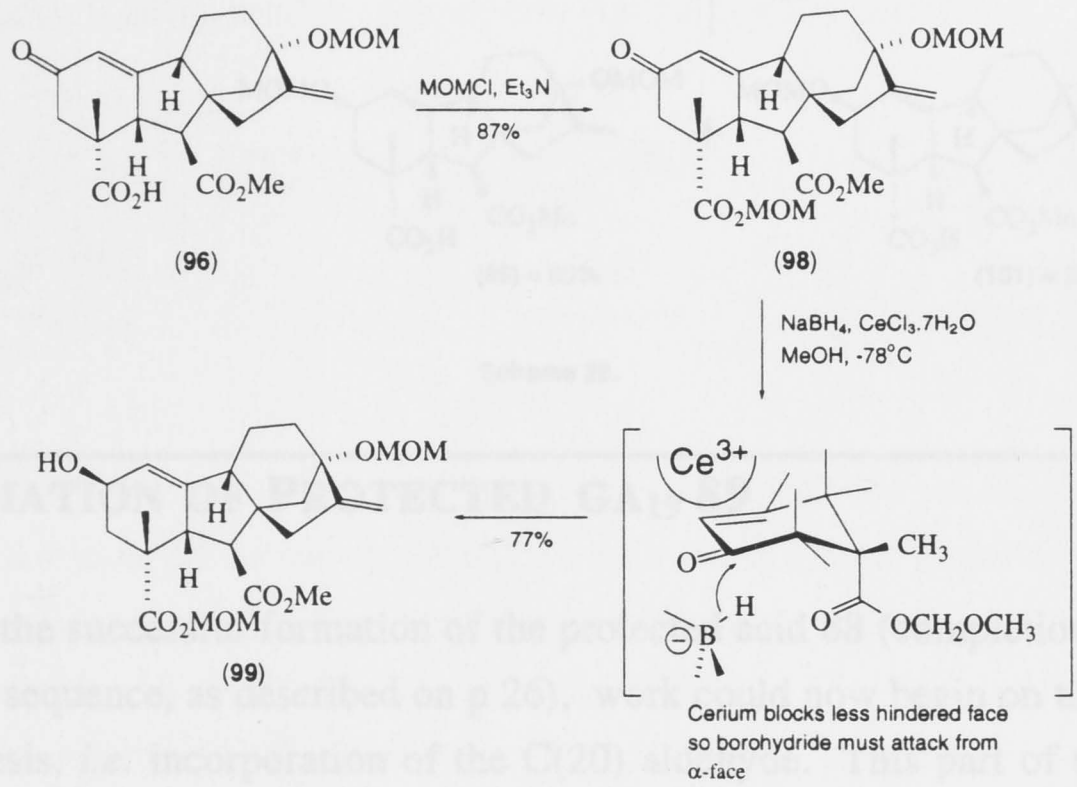
To obtain the 2β-hydroxy group, reducing agents would have to approach the carbonyl group in the enone **96** from the more hindered α-face of the gibberellin. It was thought that the C(19) acid functionality in compound **96** could assist with this reduction by directing reducing reagents to deliver the hydride to the α-face, thus giving the correct stereochemistry of the 2-hydroxy substituent.[66] However, all attempts at reducing the enone acid **96** (sodium borohydride, zinc borohydride, and lithium borohydride, in various solvents, in addition to borane in tetrahydrofuran), proceeded slowly with poor stereoselectivity (Scheme 27).



Scheme 27.

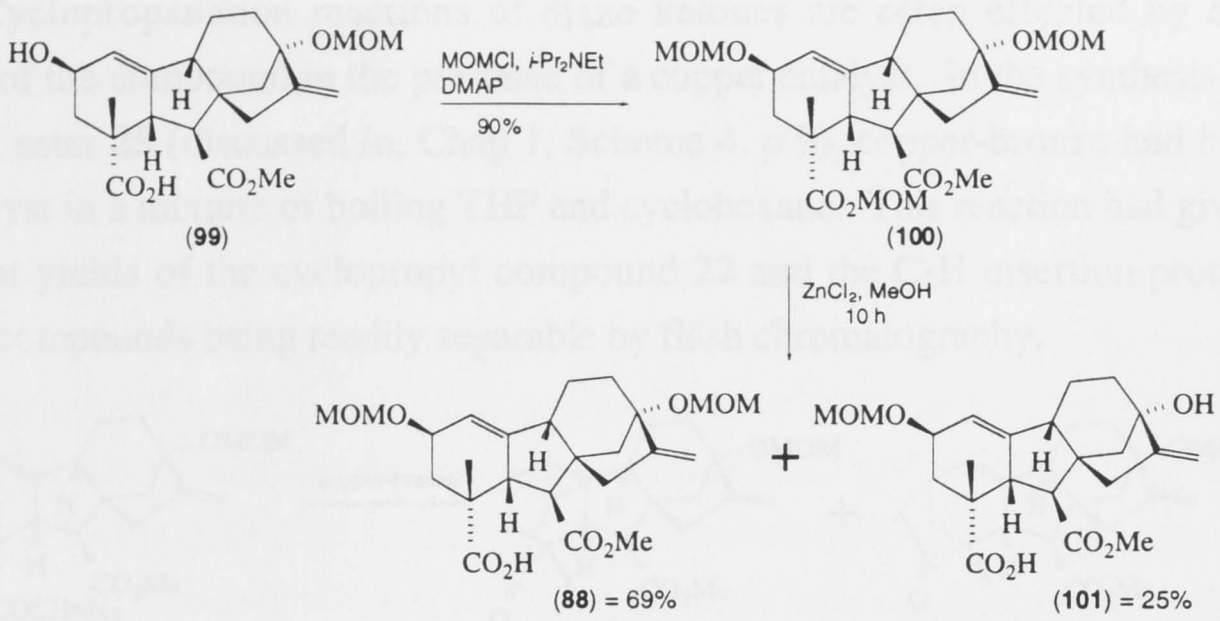
A well known method to promote hydride attack on the more hindered face of ketones involves the addition of lanthanide salts such as cerium trichloride, to the reducing system.[67] The solvated cerium salt complexes to the less hindered face of a carbonyl group (the β–face of **98**), thus blocking this face towards attack by the reducing agent (Scheme 28). Therefore, the reducing agent can only approach from the more hindered face (the α–face of **98**) of the carbonyl group.[67(b)] The reaction was attempted on the enone acid **96** and even though the correct isomer was obtained, reactions were slow and did not proceed beyond 50% conversion. It was thought that the 4-carboxy group was complexing to the carbonyl group, thereby slowing down reduction. This problem was resolved by protection of the carboxy substituent as the methoxymethyl ester. Using standard conditions,[68] the desired enone methoxymethyl ester **98** was obtained cleanly in 87% yield. Finally, treatment of **98** with an excess of dried cerium trichloride in methanol at -78°C followed by sodium borohydride, furnished the desired

2β-hydroxy compound **99** in 77% yield after chromatography. Proof for the identity of compound **99** was obtained by comparison of ^{1}H and ^{13}C NMR spectra with the spectra of the 2α-isomer. Coupling constants for the 2α-proton were difficult to obtain as they were hidden under one of the methylene signals for the 13-methoxymethoxy group.



Scheme 28.

Protection of the 2β-hydroxy compound **99** as the methoxymethyl ether proceeded smoothly under standard conditions (Scheme 29).[64] A method was now required to hydrolyse the methoxymethyl ester selectively without removing the two ether groups. The standard procedure for deprotection of methoxymethoxy groups is to treat the compound, dissolved in dry THF, with up to 10 equivalents of hydrochloric acid generated from trimethylsilyl chloride and methanol.[69] However, this method showed poor selectivity and provided mixtures of deprotected ester and/or alcohols. The use of a mild acid such as the Lewis acid, zinc chloride, was expected to be more selective.[70] Thus, after treatment of the ester **100** with a 1M solution of zinc chloride in methanol, the desired acid **88** could be obtained cleanly in 69% yield (Scheme 29). A further 25% of the material consisted of the 13-hydroxy derivative **101**. These two compounds, **88** and **101** could easily be separated by chromatography and the 13-hydroxy compound **101** then recycled through a protection/deprotection sequence.

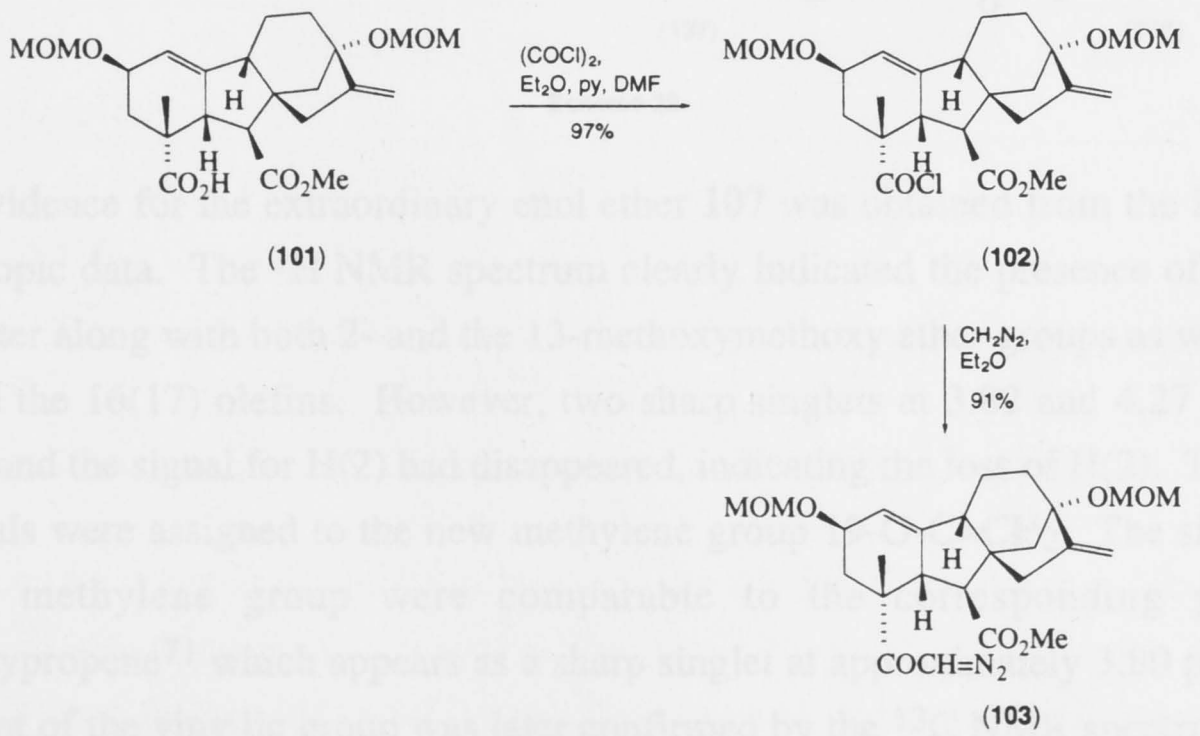


Scheme 29.

4.2.2 FORMATION OF PROTECTED GA_{19} 89

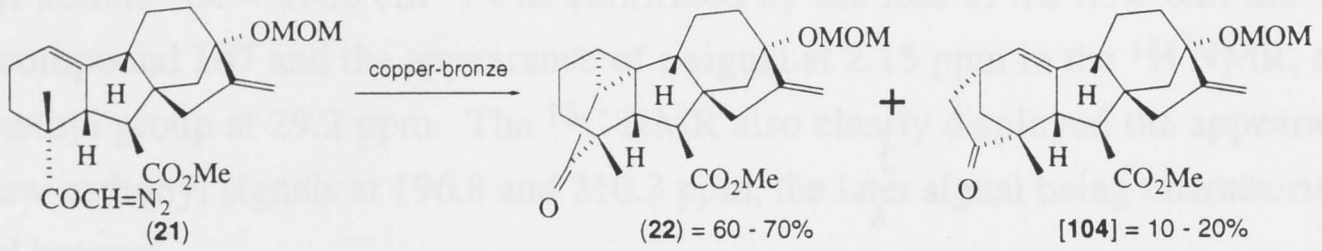
With the successful formation of the protected acid **88** (completion of part 2 of the synthetic sequence, as described on p 26), work could now begin on the third stage of the synthesis, *i.e.* incorporation of the C(20) aldehyde. This part of the sequence followed that for the synthesis of the protected GA_{19} derivative **24**, as performed by Dawe *et al.* (Scheme 4, p 9).[28]

The acid **88** was dissolved in ether and a large excess of pyridine. This solution was then added slowly to an excess of oxalyl chloride (plus a catalytic amount of DMF) in dry ether. After reaction overnight, the desired acid chloride **102** was obtained as a yellow oil in almost quantitative yield (Scheme 30). This acid chloride **102** was then added to a solution of dry diazomethane at -30°C (Scheme 30) to afford the expected diazoketone **103** in 91% yield after chromatography.



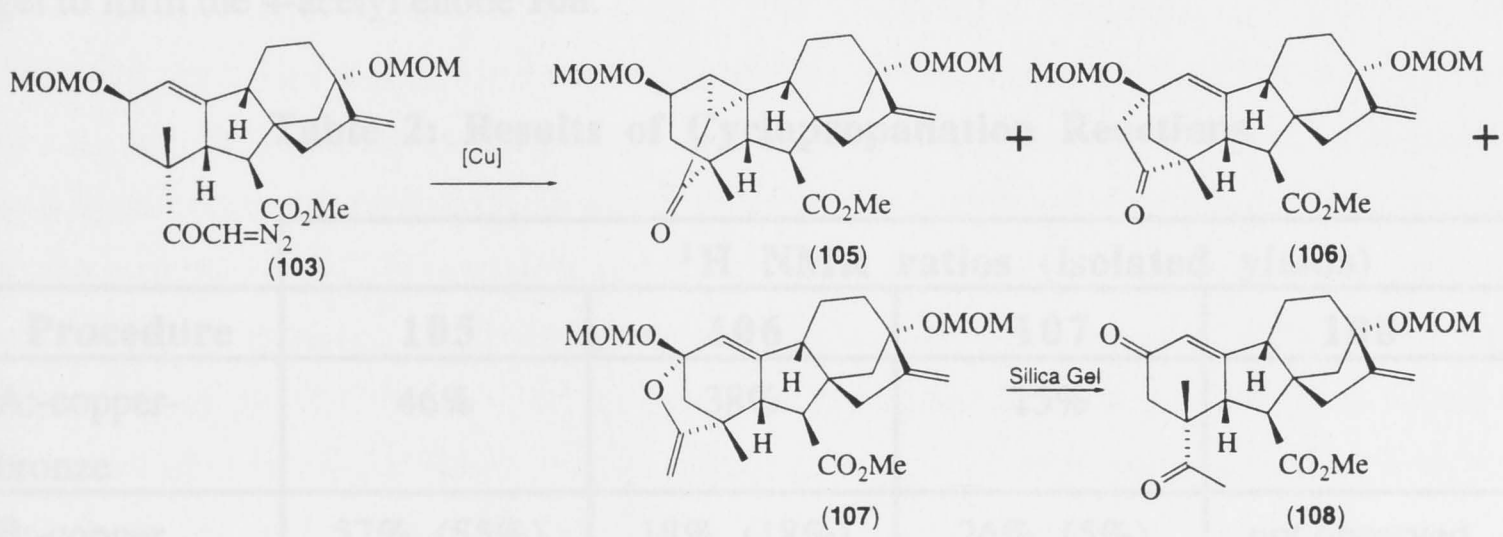
Scheme 30.

Cyclopropanation reactions of diazo ketones are often effected by heating a solution of the compound in the presence of a copper catalyst. In the synthesis of GA_{19} dimethyl ester **25** (discussed in, Chap 1, Scheme 4, p 9), copper-bronze had been used as a catalyst in a mixture of boiling THF and cyclohexane. This reaction had given fairly consistent yields of the cyclopropyl compound **22** and the C-H insertion product **104**, with the compounds being readily separable by flash chromatography.



Scheme 31.

However, the protected 2β-hydroxy diazo ketone **103** did not react as smoothly. After using the standard reaction conditions used for the synthesis of protected GA_{19} **24**, three compounds were produced with a yield of 46% for the desired cyclopropyl ketone **105** (as determined by ^1H NMR, Scheme 32, Table 2). The other compounds were found to be the expected C-H insertion product **106** along with the unusual enol ether **107**.



Scheme 32.

Evidence for the extraordinary enol ether **107** was obtained from the following spectroscopic data. The ^1H NMR spectrum clearly indicated the presence of the C(7) methyl ester along with both 2- and the 13-methoxymethoxy ether groups as well as the 1(10) and the 16(17) olefins. However, two sharp singlets at 3.82 and 4.27 ppm had appeared and the signal for H(2) had disappeared, indicating the loss of H(2). These two new signals were assigned to the new methylene group 19-O-C=CH_2. The signals for the new methylene group were comparable to the corresponding peak for 2-methoxypropene[71] which appears as a sharp singlet at approximately 3.80 ppm. The assignment of the vinylic group was later confirmed by the ^{13}C NMR spectrum which contained two new olefinic signals, as well as a very large upfield shift for C(19) to

163.3 ppm. Further evidence for the enol ether **107** was found in its decomposition product, the 4-acetyl enone **108**, the structure for which was relatively easily assigned. The IR showed the presence of three absorption bands at 1725cm^{-1}, 1700cm^{-1} and 1660cm^{-1}, consistent with the three different carbonyl groups present in the molecule. The presence of the enone (IR = 1660cm^{-1}) was confirmed by the down field shift of both H(1) in the ^{1}H NMR, and C(2) in the ^{13}C NMR spectrum. The presence of the methyl ketone (IR = 1700 cm^{-1}) was confirmed by the loss of the new olefinic signals from compound **107** and the appearance of a signal at 2.15 ppm in the ^{1}H NMR, as well as a methyl group at 29.2 ppm. The ^{13}C NMR also clearly displayed the appearance of two new carbonyl signals at 196.8 and 210.3 ppm, the later signal being characteristic for methyl ketones.

Three different copper catalysts were tested in order to optimise the yield of the desired cyclopropylketone **105**. The ratios of the crude products were determined by ^{1}H NMR spectrometry and the results from these experiments are presented in Table 2. Copper acetylacetonate was found to give the highest and most reproducible yields of the cyclopropylketone **105**. Samples were purified on silica gel and the isolated yields are displayed in brackets in Table 2. Although a small amount of the enol ether **107** was obtained for characterisation, the main bulk of the material readily decomposed on silica gel to form the 4-acetyl enone **108**.

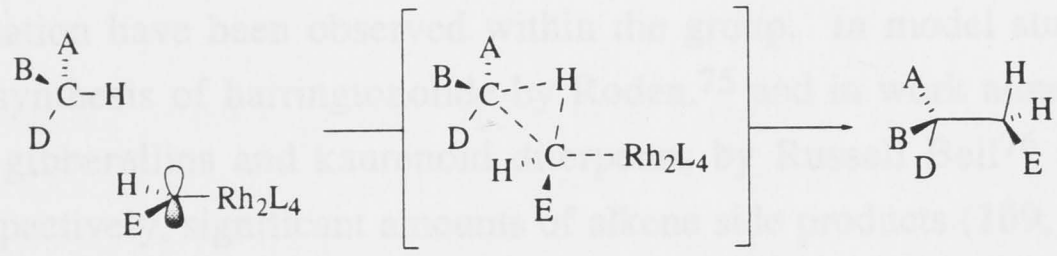
Table 2: Results of Cyclopropanation Reactions

	^{1}H NMR ratios (isolated yields)			
Procedure	**105**	**106**	**107**	**108**
A:-copper-bronze	46%	38%	15%	
B:-copper acetylacetonate	57%, (55%)	18%, (18%)	26%, (5%)	not observed (16%)
C:-t-butyl-salicylimidato-cuprate	40%	10%	50%	
D:-rhodium acetate	5%	75%, (60%)	20%	

The fourth catalyst (entry D), rhodium acetate, has been found preferentially to catalyse C-H insertion reactions in similar substrates. It was of interest to see which C-H insertion product (either **106** or **107**) would be favoured when this catalyst was utilised. The results from this experiment show that rhodium acetate preferentially forms the C-H insertion product **106** as expected.

The formation of the unstable acetyl compound **107** was very unexpected as compounds of this type have never been reported before as by-products from the transition metal catalysed reactions of diazoketones. The mechanism for the formation of this compound is related to that involved in the formation of the normal C-H insertion product **106**.

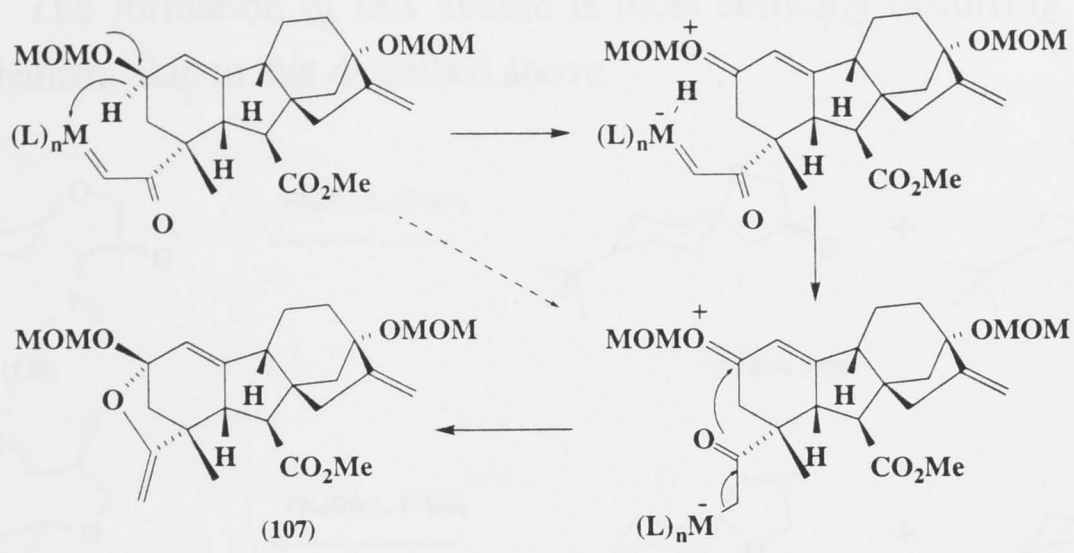
After studies on C-H insertion using rhodium catalysts, Doyle proposed that the mechanism of C-H insertion must involve a concerted, synchronous process.[72] This reaction is initiated by the overlap of the p-orbital of the metal carbene with the σ-orbital of the reacting bond resulting in C-C and C-H bond formation as the ligated metal dissociates. This mechanism was based on experimental results indicating that C-H insertion occurs with retention of configuration of the C-H bond undergoing insertion.



Mechanism for the C-H insertion Process

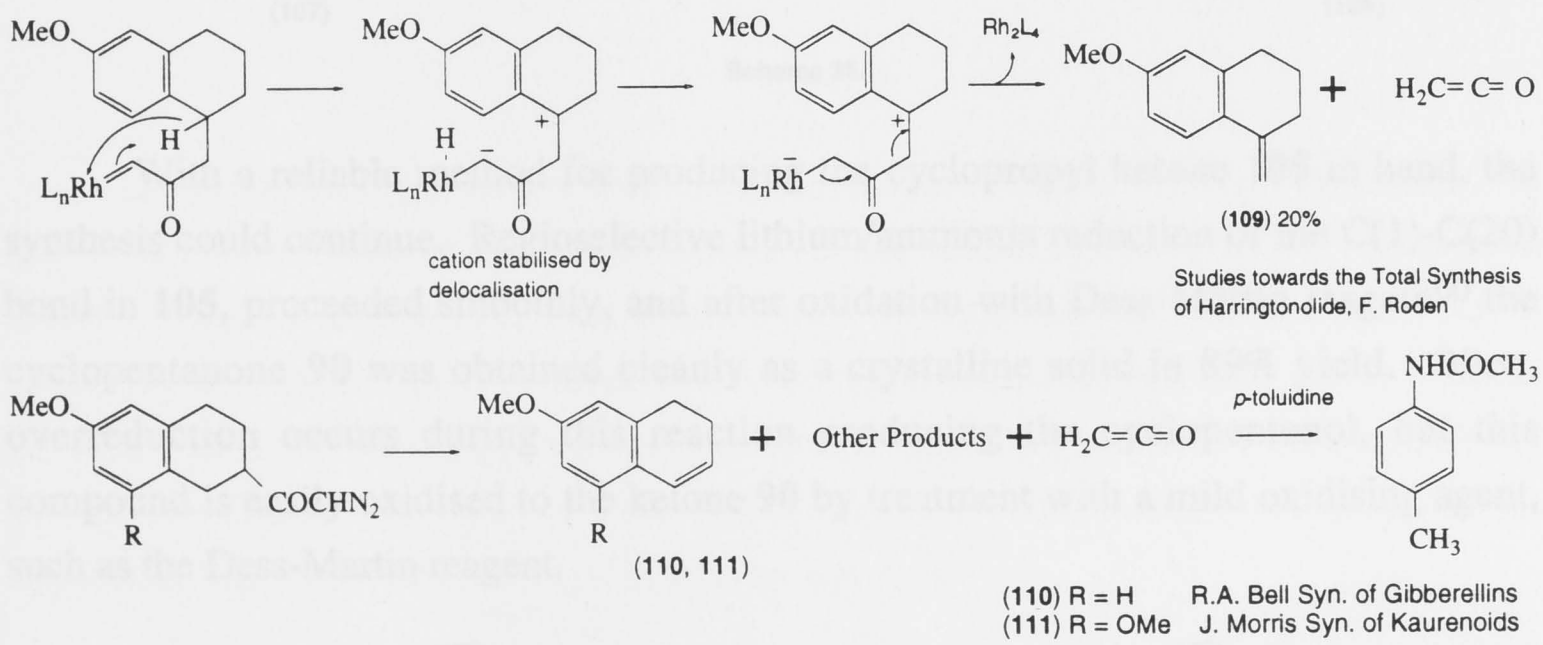
It was later found by Taber *et al.* [73] that reactivity of the target C-H insertion site followed the series methine>methylene>methyl. These results suggest the development of cationic character on the target carbon atom, the charge being stabilised by inductive and hyperconjugative electron donation from neighbouring alkyl groups. This result led to the proposal that C-H insertion may proceed *via* a concerted nonsynchronous process, with hydride transfer occurring somewhat in advance of reductive elimination and formation of the C-C bond. Further evidence to support Taber's proposal was found in the work of Adams and Spero,[74] after obtaining very high regiocontrol in C-H insertion reactions for which the C-H bond was activated by electron donating groups. In attempting to prove this theory, Adams and Spero replaced hydrogen with deuterium. The absence of a kinetic isotope effect was attributed to a late transition state along the reaction coordinate with the rate determining step occurring prior to C-H insertion.

In the formation of the enol ether **107**, hydride transfer from the 2-position of the gibberellin onto the carbenoid species (Scheme 33), independent of C-C bond formation, is almost certainly occurring. The positive charge on the 2-position is stabilised by both the 1(10) double bond, and the mesomeric effect of the methoxymethoxy group. The cationic charge is then attacked by the oxygen atom of the carbonyl group, with the resultant elimination of the metal (copper or rhodium) to afford the observed enol ether **107**.



Scheme 33.

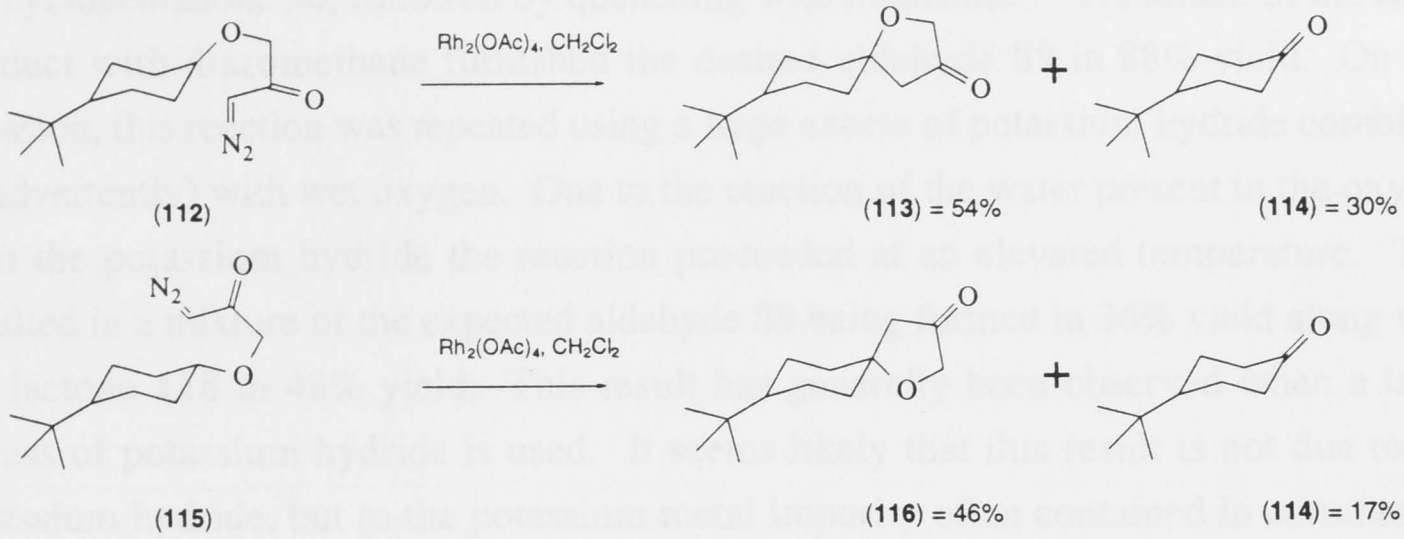
Further examples which implicate hydride transfer occurring independently of C-C bond formation have been observed within the group. In model studies directed towards the synthesis of harringtonolide by Roden,[75] and in work aimed at the total synthesis of gibberellins and kaurenoid diterpenes by Russell Bell[76] and Jonathan Morris,[77] respectively, significant amounts of alkene side products (**109**, **110** and **111**) were formed (Scheme 34). In all examples, the same hydride transfer mechanism has been implicated in their formation. If the incipient cationic centre was sufficiently stabilised, fragmentation with loss of ketene could occur, thus affording the observed alkenes. In the latter example, the formation of the ketene was substantiated by trapping with *p*-toluidine.



Scheme 34.

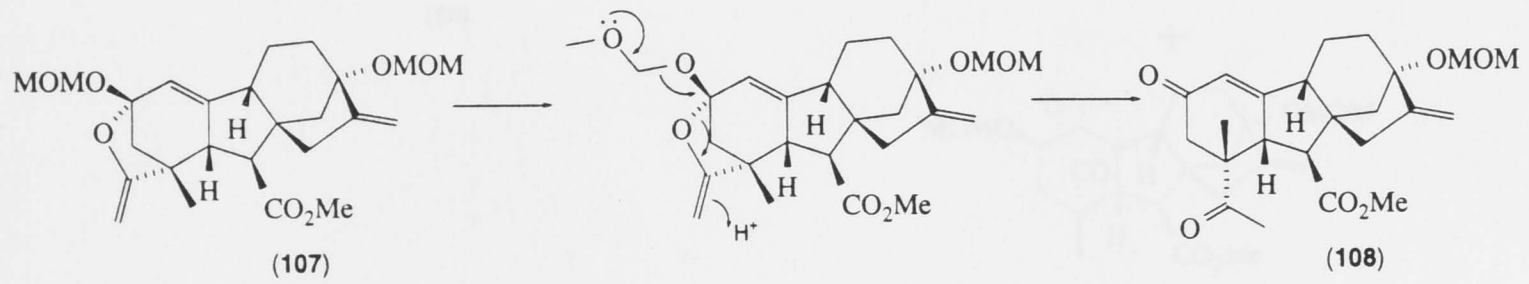
More recent examples of this process can be found in the work of Lee *et al* .[78] in studies on the formation of tertiary alcohols from secondary alcohols *via* C-H insertion (Scheme 35). In two examples given, significant amounts of a ketone by-product (**114**)

are formed. The formation of this ketone is most certainly occurring by a hydride transfer mechanism akin to that described above.*



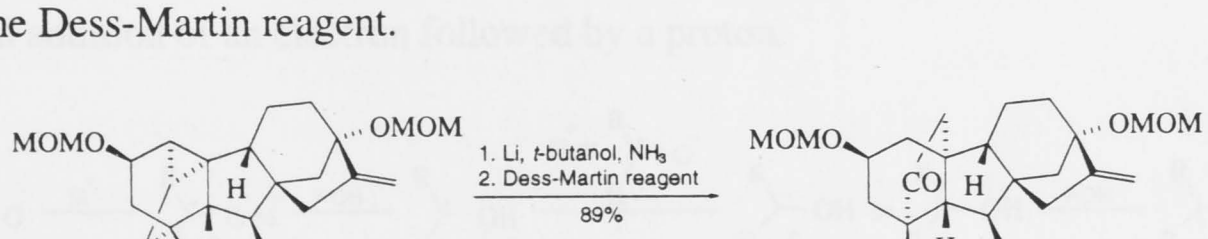
Scheme 35. Tertiary Alcohol Synthesis from Secondary Alcohols *via* C-H insertion

The stability of the enol ether **107** is very surprising as it is both vinyllic and allylic. Its decomposition to the 4-acetyl enone **108** can be easily explained (Scheme 36). Attack of a proton on the enol ether function presumably precedes opening of the acetal to form the 4-acetyl enone **108**.



Scheme 36.

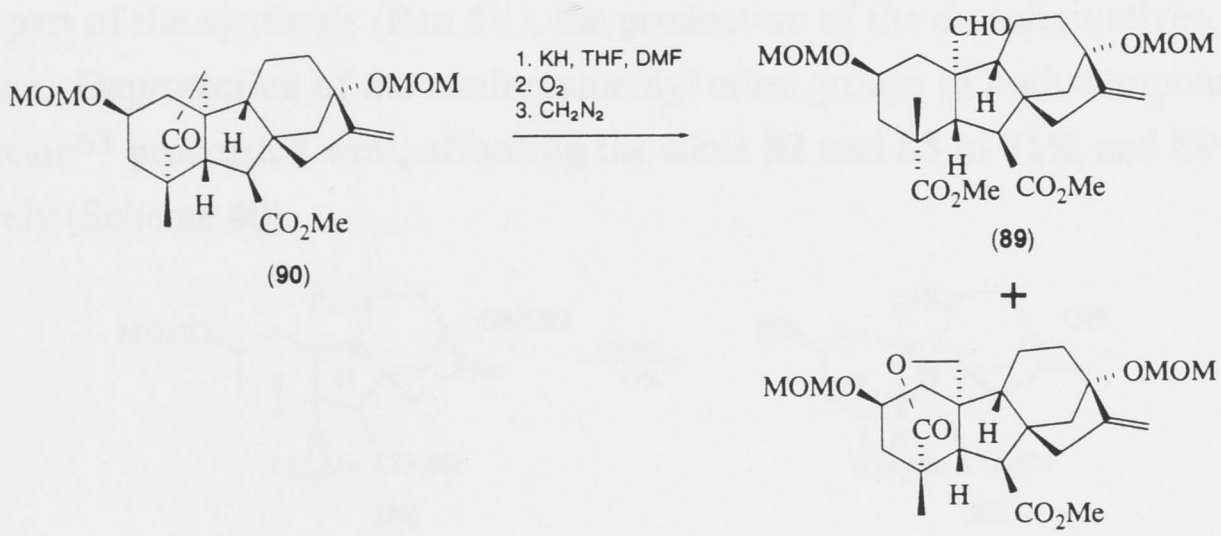
With a reliable method for producing the cyclopropyl ketone **105** in hand, the synthesis could continue. Regioselective lithium/ammonia reduction of the C(1)-C(20) bond in **105**, proceeded smoothly, and after oxidation with Dess-Martin reagent[60] the cyclopentanone **90** was obtained cleanly as a crystalline solid in 89% yield. Often, overreduction occurs during this reaction producing the cyclopentanol, but this compound is easily oxidised to the ketone **90** by treatment with a mild oxidising agent, such as the Dess-Martin reagent.



Scheme 37.

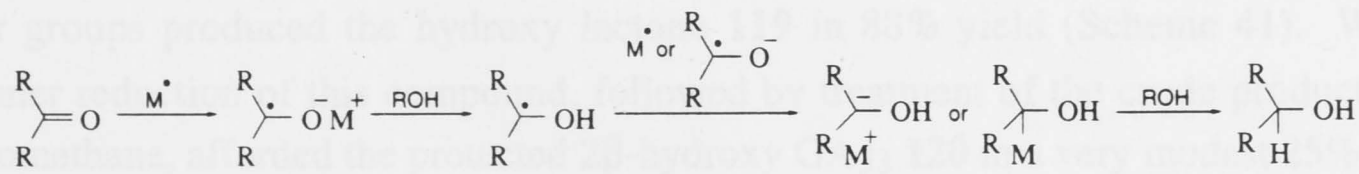
* Note added in proof: A paper published by Michael Doyle *et al.*[79] presents a different mechanism for the formation of ketone products from dirhodium(II)-catalysed diazo decomposition of secondary benzylic and allylic diazoacetates.

The next step of the synthesis was based on an unusual oxidative cleavage reaction, effected by the reaction of oxygen gas with the potassium enolate derived from the cyclopentanone **90**, followed by quenching with methanol.[28] Treatment of the crude product with diazomethane furnished the desired aldehyde **89** in 88% yield. On one occasion, this reaction was repeated using a large excess of potassium hydride combined (inadvertently) with wet oxygen. Due to the reaction of the water present in the oxygen with the potassium hydride the reaction proceeded at an elevated temperature. This resulted in a mixture of the expected aldehyde **89** being formed in 36% yield along with the lactone **118** in 48% yield. This result has generally been observed when a large excess of potassium hydride is used. It seems likely that this result is not due to the potassium hydride, but to the potassium metal impurity often contained in commercial samples of potassium hydride. Thus, the use of a large excess of potassium hydride would lead to larger quantities of potassium inadvertently being added to the reaction.



Scheme 38.

A possible explanation as to the mechanism for this result implicates the Bouveault-Blanc reaction.[80] The Bouveault-Blanc reaction applies to the reduction of esters, aldehydes and ketones with alkaline metals. This reaction can be carried out in either protic solvents such as methanol or ethanol, or aprotic solvents such as liquid ammonia or THF. Under the protic conditions there is general agreement that the mechanism follows that shown below (Scheme 39). This mechanism involves the sequential addition of an electron followed by a proton.



Scheme 39.

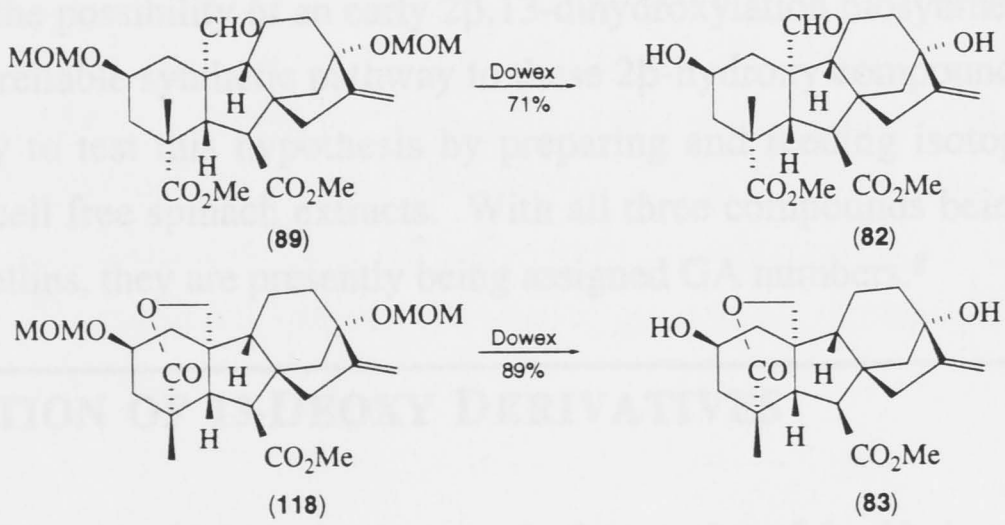
For the reaction under aprotic conditions, two mechanisms have been proposed to account for all of the products formed. One mechanism initially proposed by House,[81] then updated by Huffman *et al.*,[82] proposes that the addition of an electron to the carbonyl group forms a radical anion that exists in equilibrium with a dimeric (or higher

species). The second mechanism as originally proposed by Barton[83] and updated by Pradhan *et al.*[84] involves the direct reduction of the ketonic carbonyl group to a tetrahedral vicinal dianion. Which of the two mechanisms is correct has been hotly disputed for the past ten years.

Due to the presence of the potassium metal contamination in commercial potassium hydride, it is believed that one variant or a blend of both versions of the Blouveault-Blanc reaction is occurring. Common by-products from the Bouveault-Blanc reaction are pinacol products, but formation of the pinacol dimer of the aldehyde **89** would be unlikely, due to the steric environment of the C(20) aldehyde.

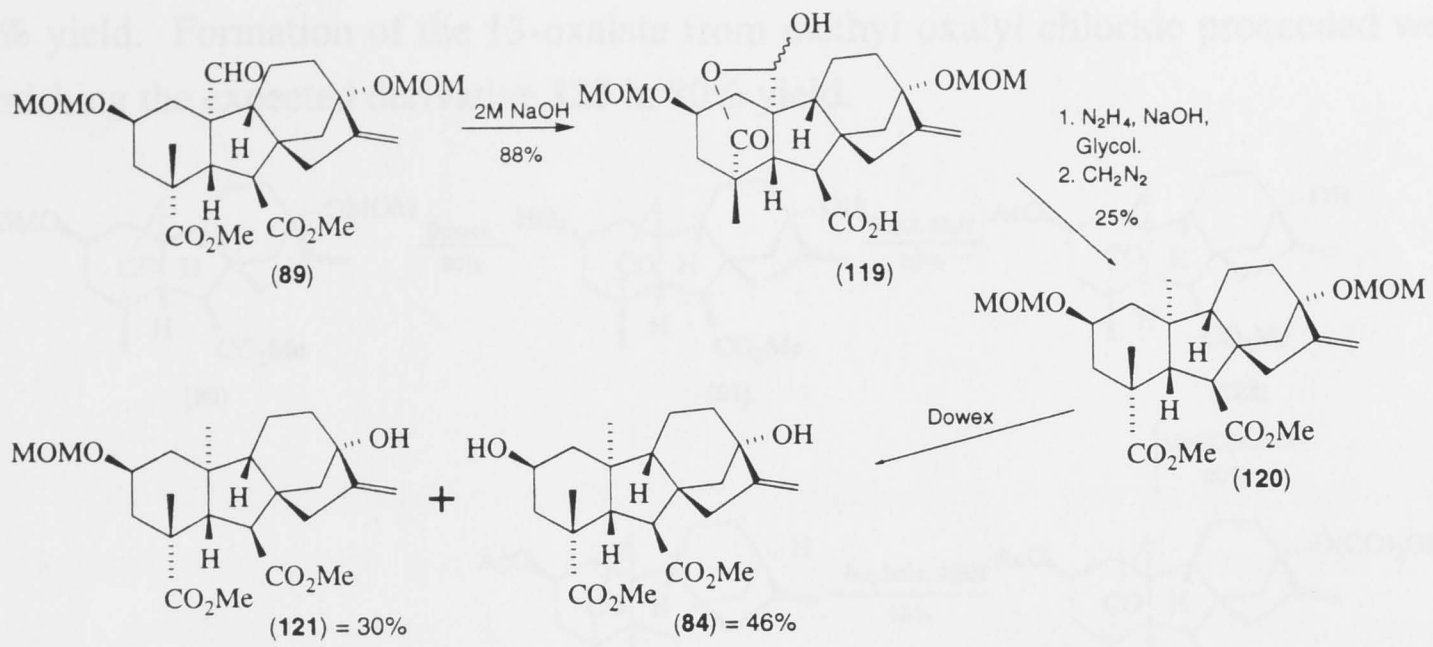
4.2.3 Formation of the Deprotected Compounds

With samples of the protected aldehyde **89** and the protected lactone **118** in hand, the final part of the synthesis (Part IV), the production of the diol derivatives, could be undertaken. Deprotection of the methoxymethyl ether groups of both compounds using Dowex resin[63] proceeded well, affording the diols **82** and **83** in 71% and 89% yields, respectively (Scheme 40).



Scheme 40.

The final compound to be synthesised was the 2β-hydroxy GA_{53} dimethyl ester **84** (Scheme 41). The pathway to this compound was based on the conditions optimised for the synthesis of the GA_{53} derivative **54** (Chap. 2, p 18). Hydrolysis of the methyl ester groups produced the hydroxy lactone **119** in 88% yield (Scheme 41). Wolff-Kishner reduction of this compound, followed by treatment of the crude product with diazomethane, afforded the protected 2β-hydroxy GA_{53} **120** in a very modest 25% yield after chromatography. Finally, treatment with Dowex resin in boiling methanol[63] yielded the desired 2β-hydroxy-GA_{53} dimethyl ester **84** in 46% yield. The remaining material from the deprotection reaction was recovered as the monoprotected compound **121**.



Scheme 41.

GCMS analysis of the trimethylsilyl derivatives of each of the three 2β-hydroxy samples **82**, **83** and **84** corresponded with derivatised natural gibberellins. It was determined that all three GAs were present in spinach. Moreover, 2β-OH GA_{53} **84** was found in pear and tomato, 2β-OH GA_{44} **83** in pea pods and maize pollen, and 2β-OH GA_{19} **82** in birch shoots. In view of the occurrence of 2β-hydroxy GAs, Zeevart[85] has speculated on the possibility of an early 2β,13-dihydroxylation biosynthetic pathway. In establishing a reliable synthetic pathway to these 2β-hydroxy compounds, there will be an opportunity to test this hypothesis by preparing and feeding isotopically labelled precursors to cell free spinach extracts. With all three compounds being confirmed as natural gibberellins, they are presently being assigned GA numbers.#

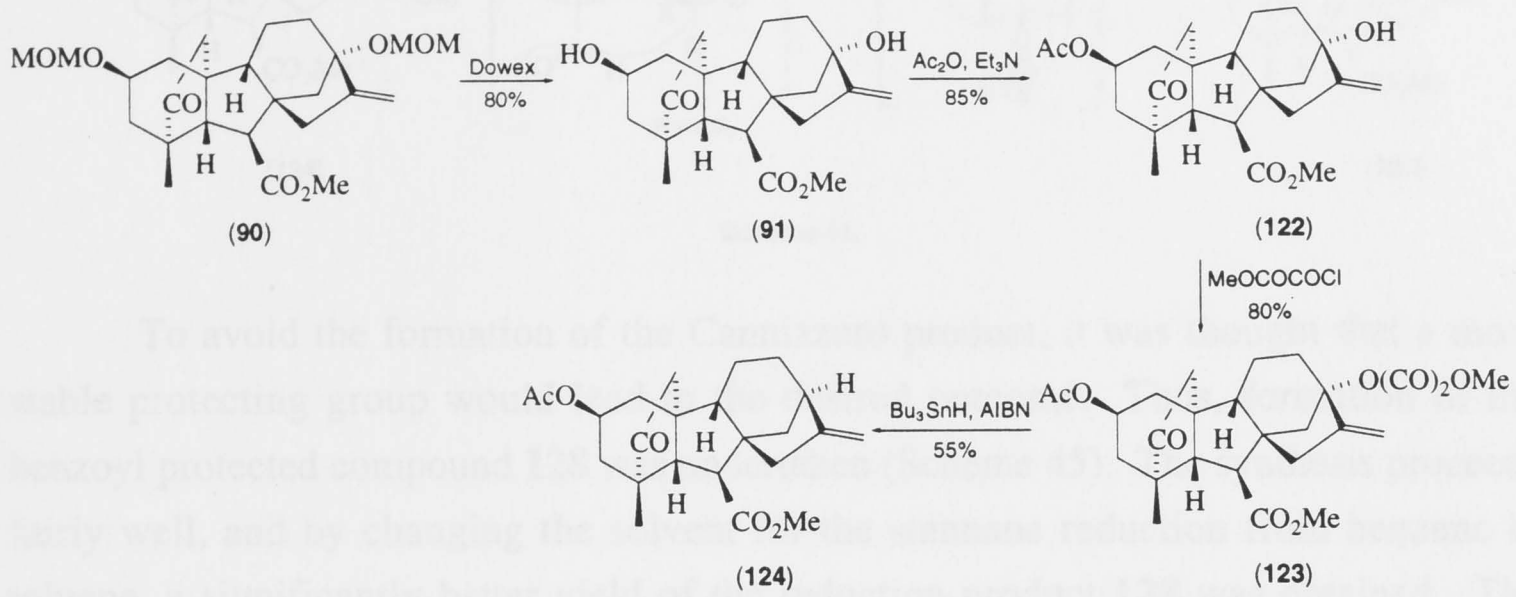
4.3 Formation of 13-Deoxy Derivatives

As explained in the introduction, synthetic samples of the 13-deoxy derivatives of the three 2β-hydroxy C(20) GAs were also required. It was thought that the cyclopentanone **90** (Scheme 25, p 27) would be the best starting point for the synthesis of these compounds. The deoxygenation of this compound could be achieved using standard radical deoxygenation of the 13-methyloxalyl derivatives.[86] With a 2-protected 13-deoxy compound **92** (Scheme 25, p 27) successfully obtained, the standard methods described above were expected to afford the desired C(20) derivatives.

Because of the expected lability of the 13-deoxy GAs towards acids, the synthesis began initially with the removal of the methoxymethoxy ether groups using Dowex resin,[63] thereby affording the diol **91** in 80% yield. Protection of the 2-hydroxyl group as the monoacetate **122** was relatively straightforward, yielding the desired product in

The author gratefully acknowledges the formation of the TMS derivatives, followed by GCMS analysis of the three compounds **82**, **83** and **84**, by Drs. Paul Gaskin and Jan Zeevart.

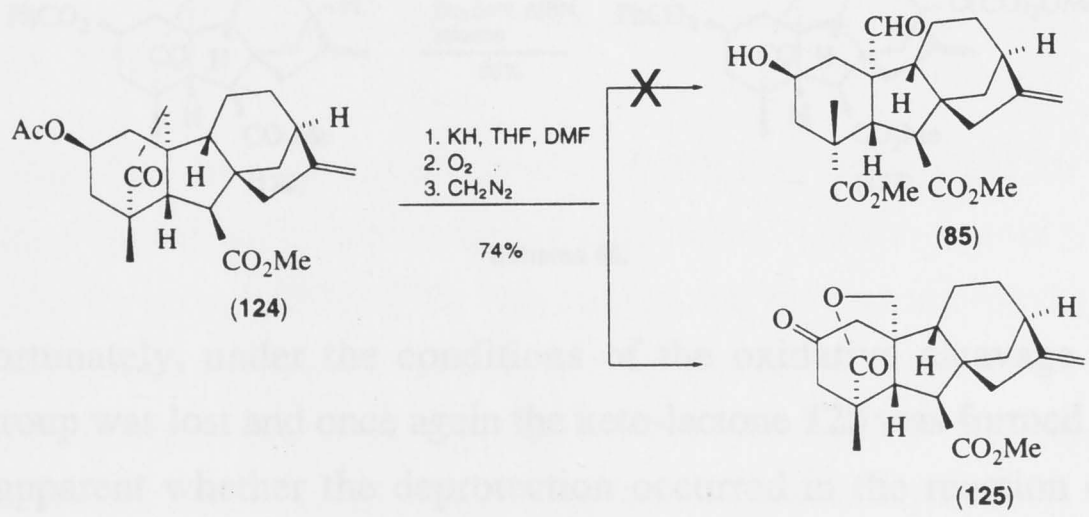
85% yield. Formation of the 13-oxalate from methyl oxalyl chloride proceeded well, furnishing the expected derivative **123** in 80% yield.



Scheme 42.

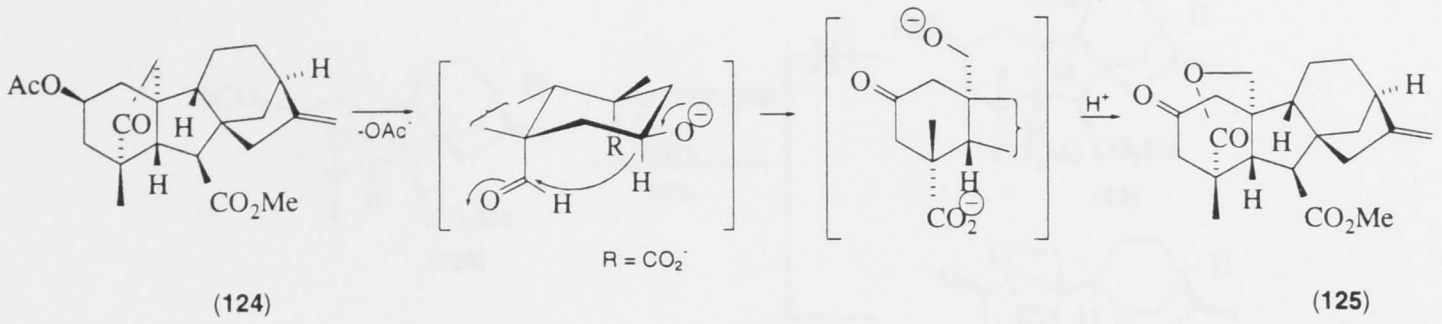
The radical deoxygenation of compound **123** was problematic, in that it took a long time (and a number of additions of AIBN) for the reaction to proceed to completion (Scheme 42). The desired 13-deoxycyclopentanone **124** was eventually obtained in 55% yield, after repeated chromatography.

It was hoped that under the conditions of the oxidative opening of the cyclopentanone **124**, the enolisable 2-acetoxy group would also be removed (Scheme 43). This would provide the desired 2β-hydroxy GA_{24} dimethyl ester **85** in one step. Unfortunately, the desired product **85** underwent an intramolecular Cannizzaro type hydride transfer,[87] presumably during the workup procedure, thereby affording the keto lactone **125** in 74% yield.



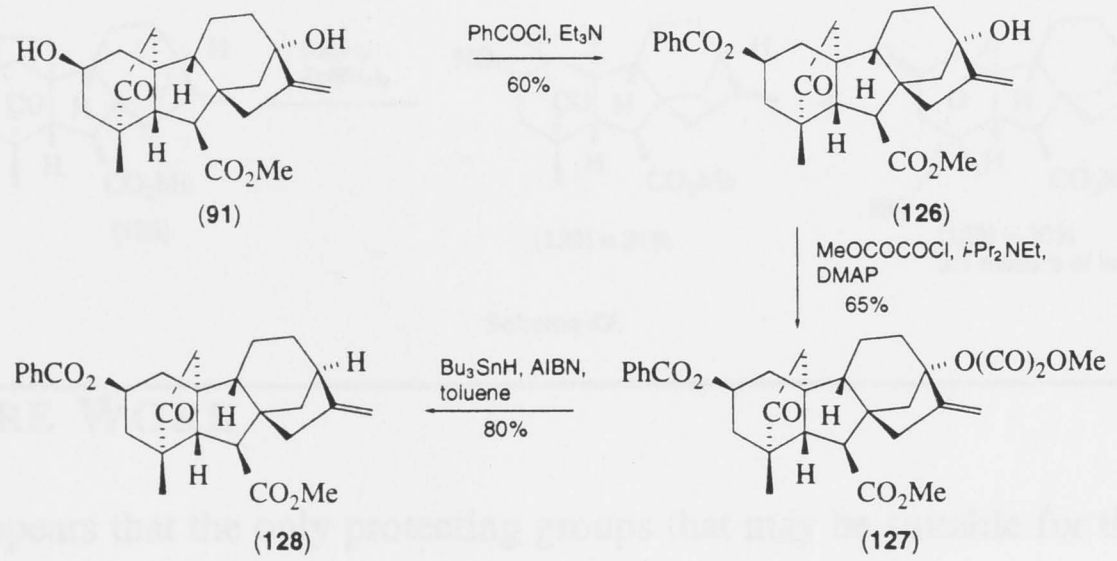
Scheme 43.

The mechanism for this intramolecular Cannizzaro type hydride transfer is shown below (Scheme 44). The desired aldehyde-alcohol **85** is presumed to form in the reaction, but under the strongly basic conditions present during quenching of the excess potassium hydride, a hydride transfer from the C(2) position to the aldehyde occurs. The hydroxy group at the C(20) position lactonises with the C(19) carboxylic acid upon acidic workup, to produce the lactone **125**.



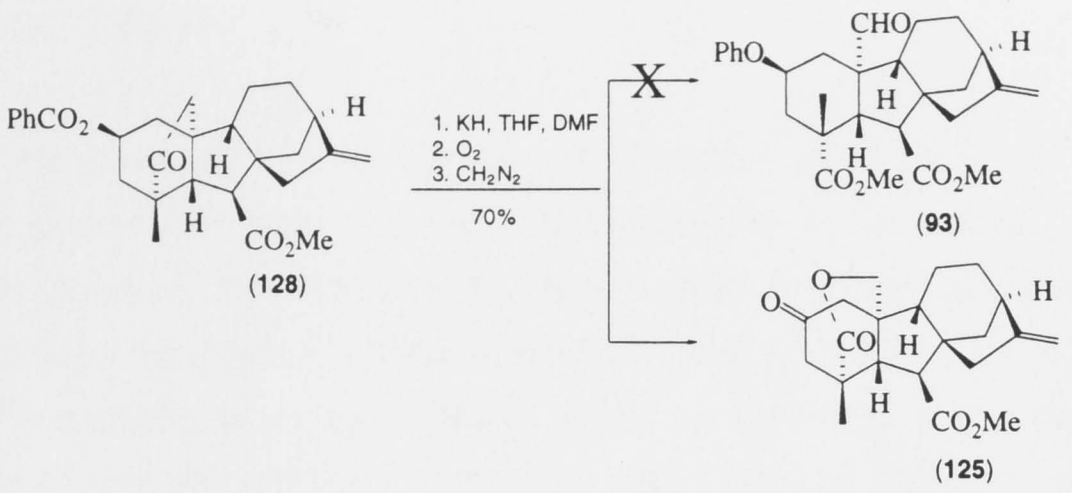
Scheme 44.

To avoid the formation of the Cannizzaro product, it was thought that a more stable protecting group would lead to the desired outcome. Thus, formation of the benzoyl protected compound **128** was undertaken (Scheme 45). The synthesis proceeds fairly well, and by changing the solvent for the stannane reduction from benzene to toluene, a significantly better yield of the reduction product **128** was obtained. The increased yield can be explained by consideration of the free energy equation: $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$.[88] In the transition state, relative to other processes that may occur, fragmentation of the tin/oxalate intermediate leads to the greatest increase in the entropy of the system. By increasing the temperature of the reaction, the entropy contribution to the overall free energy of the reaction is increased, thereby favouring the fragmentation pathway, thus providing a significantly better yield of the desired product.



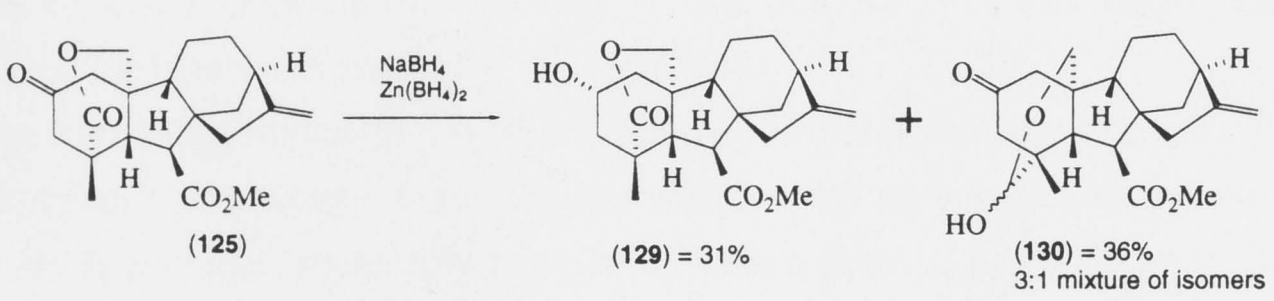
Scheme 45.

Unfortunately, under the conditions of the oxidative cleavage reaction, the protecting group was lost and once again the keto-lactone **125** was formed (Scheme 46). It was not apparent whether the deprotection occurred in the reaction or during the workup procedure. However, it was clear that hydrolysable protecting groups were unsuitable for this transformation.



Scheme 46.

It was hoped that the keto-lactone product **125** from the Cannizzaro type reaction, would be a potential precursor to the 2β-OH GA_{15} derivative **86**. Reduction of the ketone in the presence of cerium trichloride should result in the delivery of the hydride to the more hindered α-face of the molecule (as it did for the enone **98**),[67] thereby providing the desired hydroxy compound. Unfortunately, in the presence of cerium the keto-lactone **125** seemed to decompose, forming highly polar material. The use of zinc borohydride, or sodium borohydride at various temperatures (-78°C, 0°C and room temp.) only resulted in mixtures of the 2α-OH GA_{15} derivative **129** (the wrong isomer) and the lactol **130** (Scheme 47).



Scheme 47.

4.4 FUTURE WORK

It appears that the only protecting groups that may be suitable for the oxidative transformation would either be the methoxymethyl ether,[64] or the (trimethylsilyl)ethoxy-methoxy protecting group (SEM).[89] It was known that the methoxymethyl ether would be suitable for forming all three of the desired target compounds in their protected forms, but might present problems during deprotection, whereas the (trimethylsilyl)-ethyloxymethyl ether would be much easier to remove after the synthesis. However, we were unsure whether the latter protecting group could stand up to the harsh conditions of the oxidative opening reaction or the Wolff-Kishner reduction. Work on the formation of the 13-deoxy compounds **85**, **86** and **87**, using these protecting groups is presently underway. Once these compounds have been made, it is thought that all three compounds will correspond to putative gibberellins. Isotopically labelled derivatives may also be required for studies on the biosynthetic interconversions of these compounds.

CHAPTER FIVE

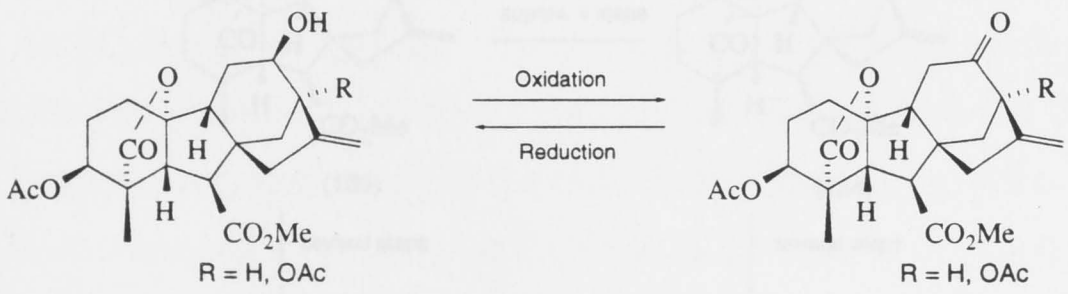
12-HYDROXY C-20 GIBBERELLINS

5.1 INTRODUCTION

There are presently 16 known, naturally occurring 12-hydroxy C-19 GAs. Until recently, these compounds have been the most inaccessible of the natural gibberellins in terms of both isolation and synthesis.[90] Reasonably firm identification of several structures had been established by the microbiological transformation of 12-hydroxy kaurenoids,[91] but confirmation by synthesis would be desirable. In the present study it was of interest to produce synthetic samples of both 12α- and 12β-hydroxy C-20 GAs, as it was believed that a number of these compounds could be putative natural gibberellins.

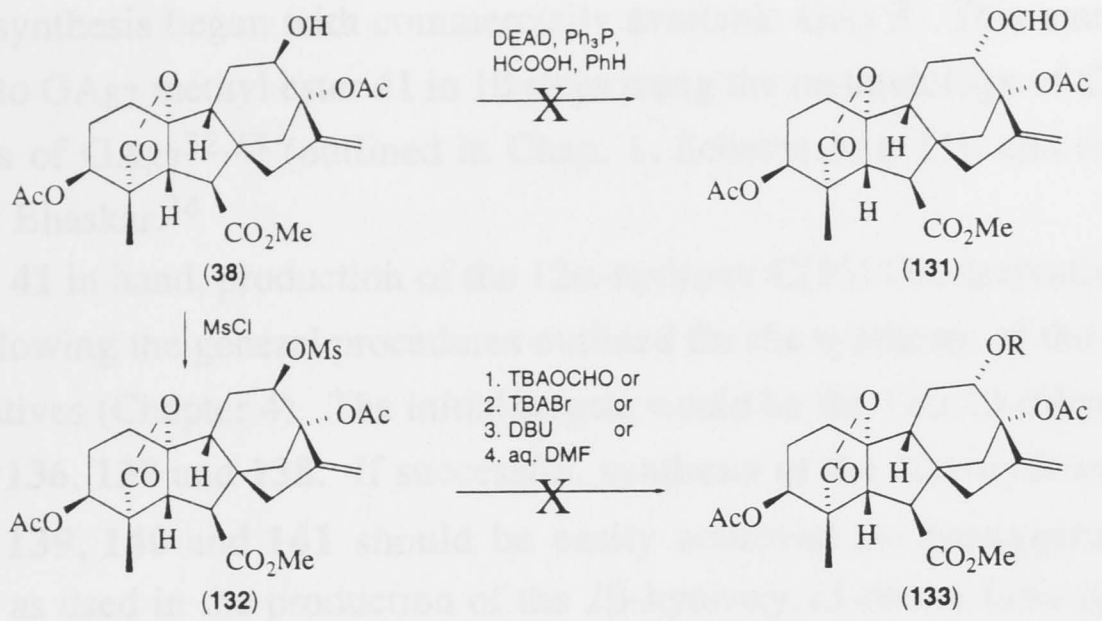
Relatively secure identifications had already been made for the derivatised 12β-hydroxy compounds, 12β-hydroxy GA_{24}, 12β-hydroxy GA_{15} and 12β-hydroxy GA_{12} (methyl ester derivatives **145**, **146** and **147**, in Scheme 50). Assignment of these new GAs was of considerable interest as they had been isolated from a number of different plant sources.[92] However, a more speculative identification of the dihydroxy GA, 12α-hydroxy GA_{19} (dimethyl ester derivative **136**, in Scheme 50) had also been made from a fraction isolated from canola (*Brassica campestris*). Several 12-hydroxy C-19 GAs had previously been isolated from canola,[93] and the identification of 12-hydroxy C-20 GAs in this species would help resolve the many questions surrounding the biosynthesis of the C-19 derivatives.

In attempting to design a synthetic pathway towards these compounds, it was of great importance to choose a sequence that would allow easy access to as many of the derivatives as possible, preferably from an advanced intermediate. Previously, Chu[94] had demonstrated that the reduction of the 12-oxo GAs afforded only the 12β derivatives (Scheme 48).



Scheme 48.

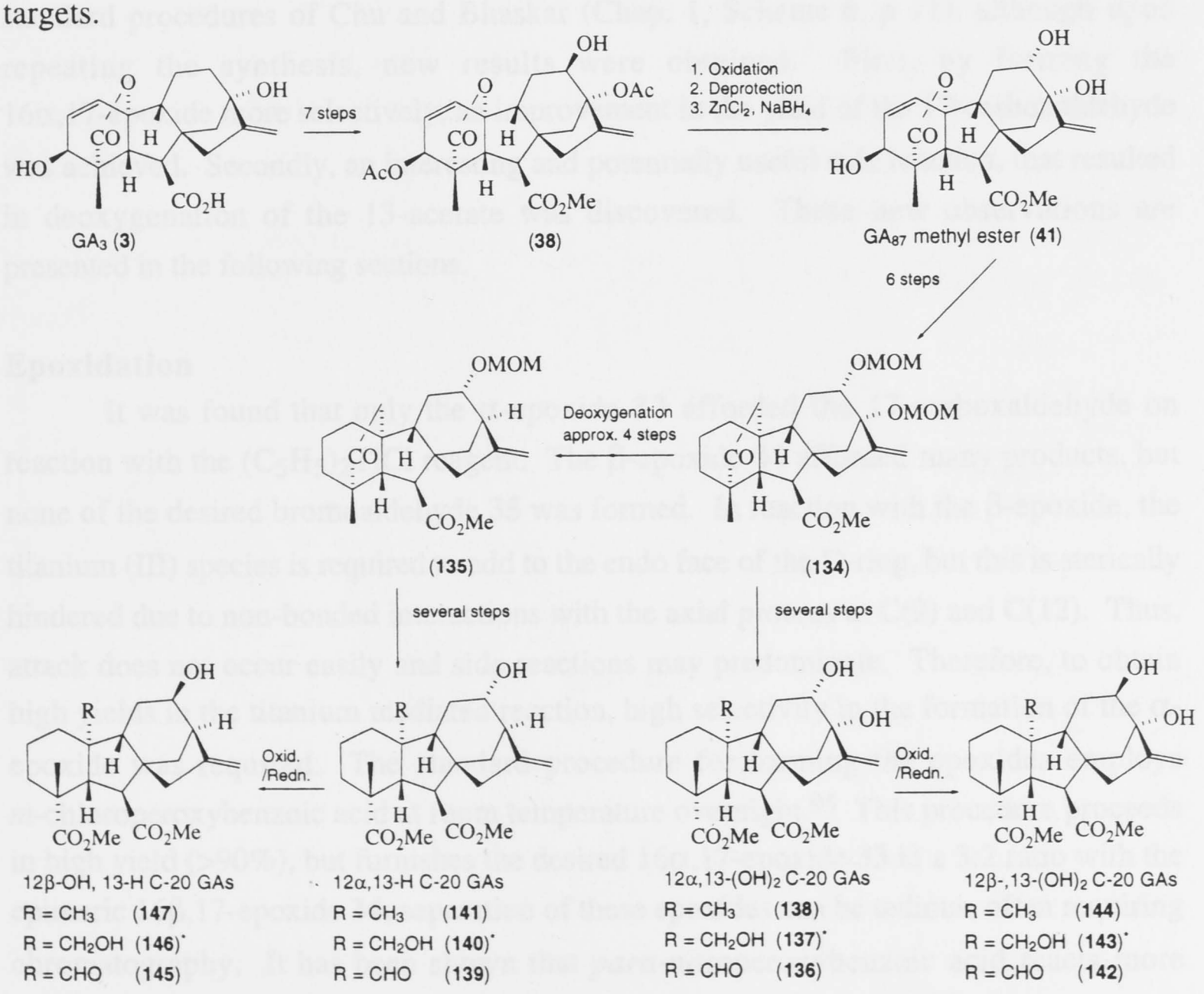
Moreover, attempts to invert the stereochemistry of the 12β derivatives *via* displacement of the 12β-mesylate in compound **132**, or by means of the Mitsunobu process were unsuccessful (Scheme 49). It was possible to prepare 12α-epimers successfully only by reducing chelated derivatives of 13-hydroxy-12-oxo intermediates (Scheme 6, p 11).



(38) (131) (132) (133)

Scheme 49. Attempted Isomerisation of 12β-hydroxy GAs

It was believed, therefore, that the most secure and efficient route to the synthesis of all of these compounds would involve the synthesis of the protected 12α,13-dihydroxy intermediate **134** (Scheme 50). Such a compound (as the common intermediate), would provide access to all of the possible variants, even though this sequence would involve a "double inversion" of stereochemistry at C-12 for some of the targets.



GA_3 (**3**) (**38**) GA_{87} methyl ester (**41**)

(**135**) (**134**)

12β-OH, 13-H C-20 GAs
R = CH_3 (**147**)
R = CH_2OH (**146**)*
R = CHO (**145**)

12α,13-H C-20 GAs
R = CH_3 (**141**)
R = CH_2OH (**140**)*
R = CHO (**139**)

12α,13-$(OH)_2$ C-20 GAs
R = CH_3 (**138**)
R = CH_2OH (**137**)*
R = CHO (**136**)

12β-,13-$(OH)_2$ C-20 GAs
R = CH_3 (**144**)
R = CH_2OH (**143**)*
R = CHO (**142**)

Scheme 50. Planned Synthetic Sequence to 12-hydroxy C-20 GAs

* Isolated as the lactone.

The synthesis began with commercially available GA_3 **3**. This material can be converted into GA_{87} methyl ester **41** in 10 steps using the methodology of Chu *et al.* for the synthesis of GA_{87}[32,33] (outlined in Chap. 1, Scheme 6, p 11), and subsequently improved by Bhaskar.[34]

With **41** in hand, production of the 12α-hydroxy C(20) GA derivatives could be achieved following the general procedures outlined for the syntheses of the 2β-hydroxy C(20) derivatives (Chapter 4). The initial targets would be the 12α,13-dihydroxy C(20) compounds **136**, **137** and **138**. If successful, synthesis of the 12α-hydroxy,13-deoxy derivatives **139**, **140** and **141** should be easily achieved by deoxygenation of the 13-oxalates, as used in the production of the 2β-hydroxy,13-deoxy GAs (explained in Chap. 4, p 39 and 40). Finally, formation of the 12β,13-dihydroxy derivatives **142**, **143** and **144**, as well as the 12β,13-deoxy compounds **145**, **146** and **147** could be accomplished relatively easily *via* an oxidation/reduction cycle of the 12α-isomers.

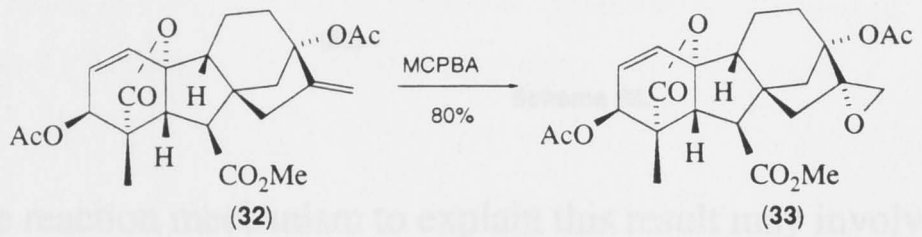
5.1.1 Synthesis of GA_{87} Methyl Ester 41

The sequence for the synthesis of the starting GA_{87} methyl ester **41**, followed the standard procedures of Chu and Bhaskar (Chap. 1, Scheme 6, p 11), although upon repeating the synthesis, new results were obtained. First, by forming the 16α,17-epoxide more selectively, an improvement in the yield of the 17-carboxaldehyde was achieved. Secondly, an interesting and potentially useful side reaction, that resulted in deoxygenation of the 13-acetate was discovered. These new observations are presented in the following sections.

Epoxidation

It was found that only the α-epoxide **33** afforded the 17-carboxaldehyde on reaction with the $(C_5H_5)_2TiCl$ reagent. The β-epoxide **34** afforded many products, but none of the desired bromoaldehyde **35** was formed. In reaction with the β-epoxide, the titanium (III) species is required to add to the endo face of the D-ring, but this is sterically hindered due to non-bonded interactions with the axial protons at C(9) and C(12). Thus, attack does not occur easily and side reactions may predominate. Therefore, to obtain high yields in the titanium mediated reaction, high selectivity in the formation of the α-epoxide was required. The standard procedure for forming the epoxides employs *m*-chloroperoxybenzoic acid at room temperature overnight.[95] This procedure proceeds in high yield (>90%), but furnishes the desired 16α,17-epoxide **33** in a 3:2 ratio with the epimeric 16β,17-epoxide **34**; separation of these epoxides can be tedious, often requiring chromatography. It has been shown that *para*-nitroperoxybenzoic acid reacts more slowly with the diacetate **32**, and is therefore much more selective.[96] Reaction of the protected GA_3 **32** with this reagent forms the α-epoxide **33** almost exclusively, but

para-nitroperoxybenzoic acid is expensive to obtain commercially and its synthesis can be troublesome. It was found that, by lowering the temperature of the reaction with *m*-chloroperoxybenzoic acid (initially at -15°C and left to slowly warm up to 4°C), the reaction proceeded in a much more selective manner (although at a much slower rate, requiring up to 4 days to proceed to completion), producing the desired pure α-epoxide **33** in 80% yield after one recrystallization. A further 10-15% of the desired α-epoxide could be obtained by chromatography of the mother liquor.

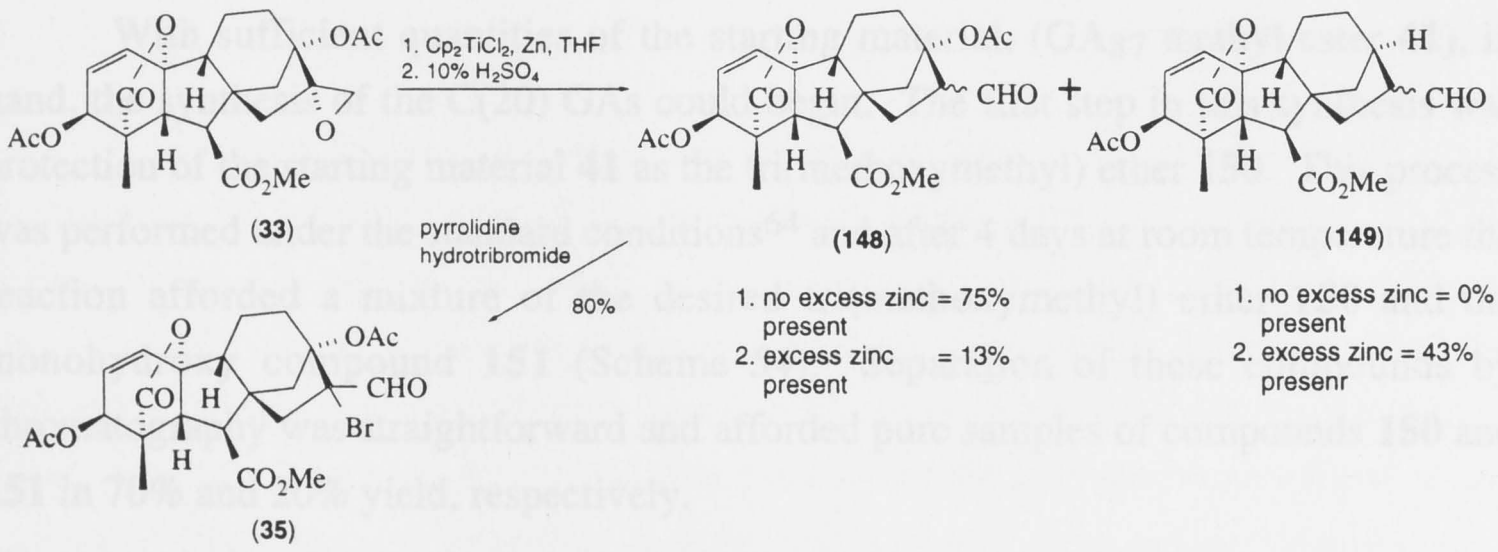


(32) **(33)**

Scheme 51.

13-Deoxygenation

In attempting to improve the synthesis of the bromoaldehyde **35**, instead of *in situ* bromination, a two step procedure was investigated. This process involved opening the epoxide with the $(C_5H_5)_2TiCl$ reagent, followed by quenching with mineral acid to form the aldehyde **148** (Scheme 52). This aldehyde could then be brominated under standard conditions[97] to afford the expected bromoaldehyde **35** in 60% yield over the two steps.

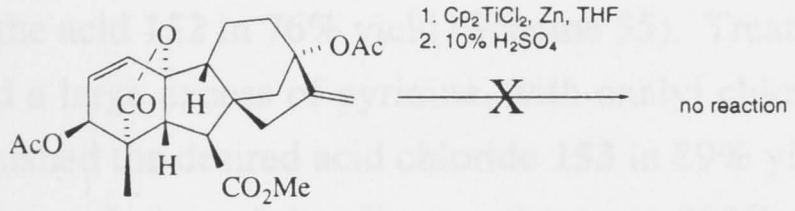


(33) **(148)** **(149)** **(35)**

Scheme 52.

However, it was found that if the epoxide **33** was added to the titanium reagent in the presence of excess zinc powder (used to reduce the titanium (IV) reagent to the reactive titanium (III) species), upon quenching the reaction with mineral acid, the aldehyde **148** and its 13-desacetoxy derivative **149** were obtained in 13% and 41% yield, respectively (Scheme 52). Prevention of the deacetoxylation could easily be achieved by adding the preformed titanium reagent to the gibberellin (so no zinc was

present in the reaction).# It was found that this deacetoxylation required both zinc and titanium to occur, and it would not occur on the parent 16,17 olefinic bond in compound **32** (Scheme 53).



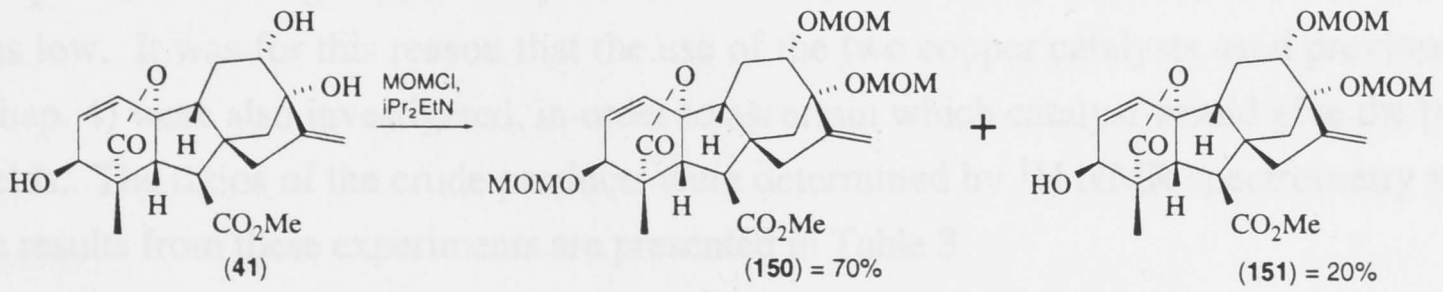
(32)

Scheme 53.

A possible reaction mechanism to explain this result may involve complexation of the titanium (IV) 16-en-17-olate to the 13-acetoxy group, thereby assisting a strongly reducing agent eg. a titanium species in a lower oxidation state [e.g. Ti(II) can be formed by the disproportion of 2xTi(III)],[99] or maybe zinc itself, to attack the acetoxy group. This second reactive species reduces the acetoxy group, transferring an electron into the relatively low lying π^* orbital of the carbonyl group. Fragmentation of this excited species produces a tertiary radical which can be reduced by another electron from titanium (III), followed by protonation to form the deoxy compound **149**.

5.2 Synthesis of 12α,13-Dihydroxy Gibberellins

With sufficient quantities of the starting material, (GA_{87} methyl ester **41**), in hand, the synthesis of the C(20) GAs could begin. The first step in this synthesis was protection of the starting material **41** as the tri(methoxymethyl) ether **150**. This process was performed under the standard conditions[64] and after 4 days at room temperature the reaction afforded a mixture of the desired tri(methoxymethyl) ether **150** and the monohydroxy compound **151** (Scheme 54). Separation of these compounds by chromatography was straightforward and afforded pure samples of compounds **150** and **151** in 70% and 20% yield, respectively.



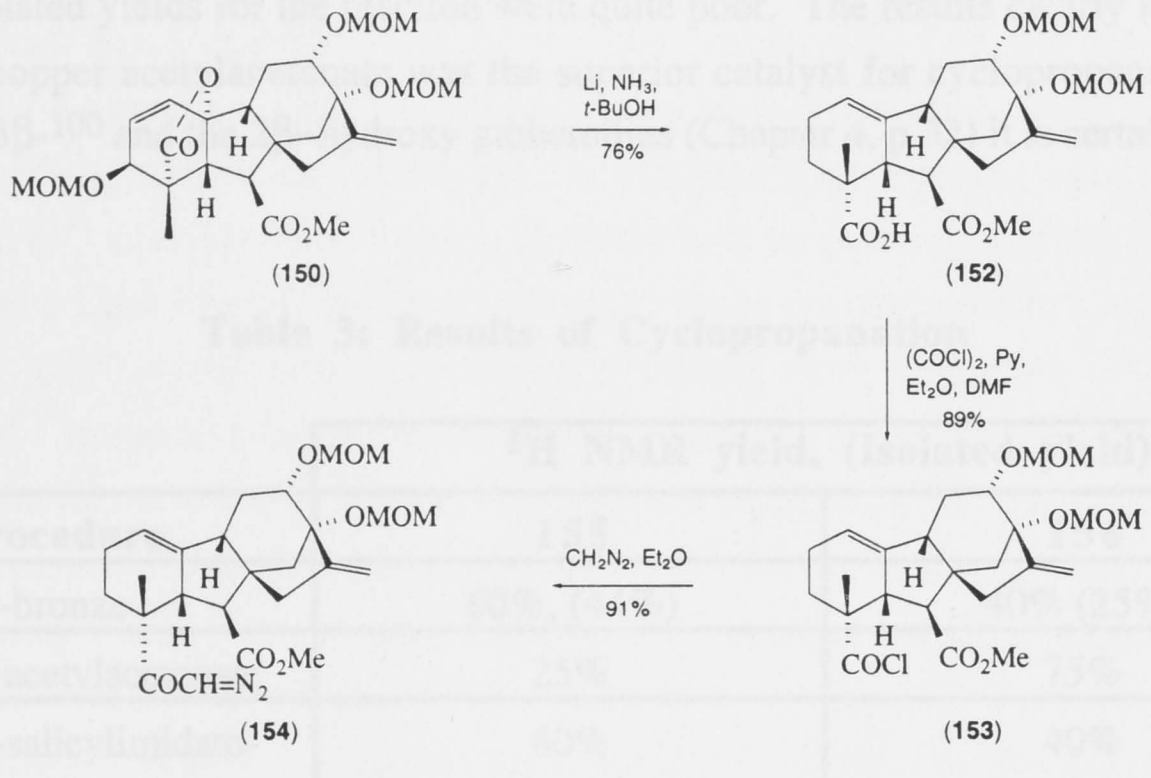
(41) (150) = 70% (151) = 20%

Scheme 54.

This deacetoxylation reaction was studied further within the group by Bhaskar,[98] who optimised the yield of the deacetoxylation to 80%.

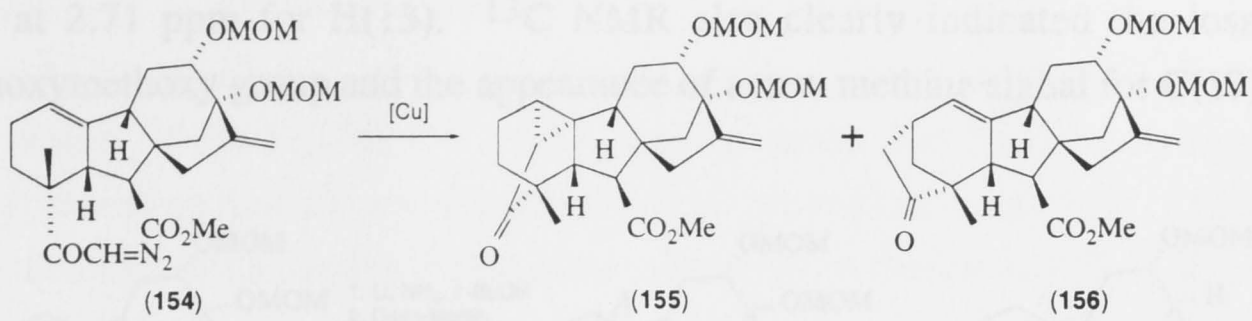
The low reactivity of the 3-hydroxy group is rather surprising. Attempts at forcing the reaction to go to completion failed, but after purification and separation, compound **151** could be resubmitted to the protection step under the standard conditions.

Dissolving metal reduction of compound **150** using lithium/ammonia proceeded smoothly to produce the acid **152** in 76% yield (Scheme 55). Treatment of the acid **152** dissolved in ether and a large excess of pyridine, with oxalyl chloride (plus a catalytic amount of DMF) furnished the desired acid chloride **153** in 89% yield. Compound **153** was then treated with a solution of dry diazomethane at -30°C, giving the expected diazoketone **154** in 91% yield after chromatography.



Scheme 55.

It had been found that copper acetylacetonate was a far superior catalyst for effecting the cyclopropanation of the 3β-hydroxy series, with approximately 20-30% improvement in the yield over other catalysts such as copper-bronze or *t*-butylsalicylimidato cuprate.[100] Copper acetylacetonate was also found to afford the highest yield of the desired cyclopropyl ketone for the protected 2β-hydroxy compounds (Chap. 4, p 32). However, for the cyclopropanation of the 12α-methoxymethoxy diazo compound **154** using copper acetylacetonate, the yield of the desired cycloproyl ketone was low. It was for this reason that the use of the two copper catalysts used previously (Chap. 4) were also investigated, in order to ascertain which catalyst would give the best yields. The ratios of the crude products were determined by ^{1}H NMR spectrometry and the results from these experiments are presented in Table 3.



(154) (155) (156)

Scheme 56.

With no activating group at C(2) in the gibberellin (Chapter 4, p 32), only the expected cyclopropyl compound **155** and the C-H insertion product **156** were obtained, but the isolated yields for the reaction were quite poor. The results clearly indicate that although copper acetylacetonate was the superior catalyst for cyclopropanation of the protected 3β-[100] and the 2β–hydroxy gibberellins (Chapter 4, p 32) it is certainly inferior here.

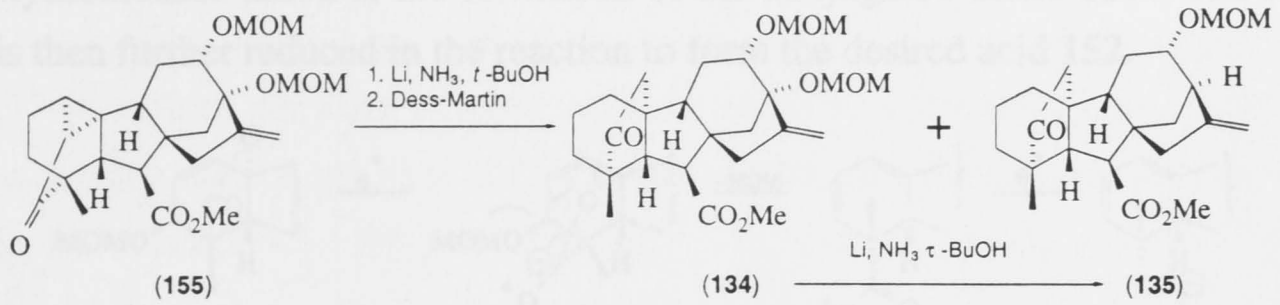
Table 3: Results of Cyclopropanation

	^{1}H NMR yield, (Isolated yield)	
Procedure	**155**	**156**
A: copper-bronze	60%, (44%)	40% (25%)
B: copper acetylacetonate	25%	75%
C: t-butyl-salicylimidato-cuprate	60%	40%

After regioselective lithium/ammonia reduction of the C(1)-(20) bond of the cyclopropyl ketone **155**, using a slight excess of lithium, the crude material was oxidised with Dess-Martin reagent.[60] This oxidation was necessary to convert any cyclopentanol formed in the reaction (by overreduction) to cyclopentanone. Surprisingly, the Birch reduction furnished the 13-deoxy cyclopentanone **135** along with the expected cyclopentanone **134**, in 50% and 38% yields, respectively (Scheme 57). The formation of the 13-deoxy compound **135** was very unexpected, but this serendipitous outcome allowed easy access to the 13-deoxy derivatives **139**, **140** and **141** (Scheme 50, p 44). Therefore, the number of steps required to synthesise these compounds was significantly reduced (discussion on the synthesis of the 13-deoxy series will be continued in the next section).

Proof of the structure for **135** was obtained by a number of spectroscopic techniques. The mass spectra contained a molecular ion of *m/z* 388 which is consistent with the loss of *m/z* 60 ($C_2H_4O_2$), from the di(methoxymethoxy) compound **134** (**134**, molecular ion m/z = 448). In the ^{1}H NMR spectra, signals for only one methoxymethoxy group was apparent, coupled with the appearance of a characteristic

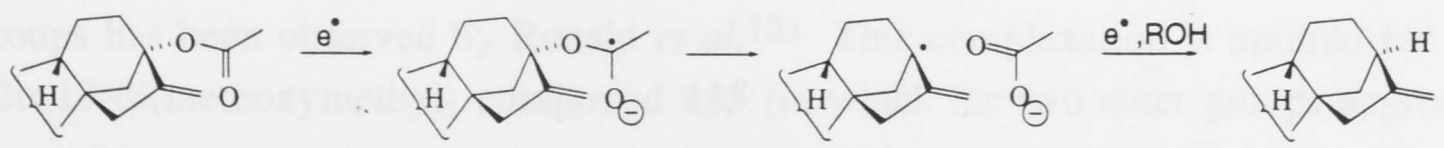
doublet at 2.71 ppm for H(13). ^{13}C NMR also clearly indicated the loss of the 13-methoxymethoxy group and the appearance of a new methine signal for C(13) at 46.5 ppm.



Scheme 57.

It was found that the ratio of the two compounds **134** and **135** could be controlled by the amount of lithium metal being added to the reaction. High yields (78%) of the di(methoxymethyl) ether **134** could be obtained if the reaction was stopped after the addition of 2 equivalents of lithium. Reaction with an excess of lithium (followed by oxidation with Dess-Martin), however, resulted only in the mono(methoxymethyl) ether compound **135**, mixed with compounds resulting from reduction of the 7-ester functionality. It was also found that the di(methoxymethyl) ether **134** could be converted into the mono(methoxymethyl) ether **135** by Birch reduction (followed by oxidation of the C(19) carbinol function), although the yield for this transformation was low (approximately 40%). These results indicate that the cyclopropyl group is reduced before the reductive removal of the 13-methoxymethoxy group. However, the 13-deoxygenation seems to compete with reduction of the cyclopentanone to the cyclopentanol.* Finally, the C(7) methyl ester group is reduced to the carbinol function.

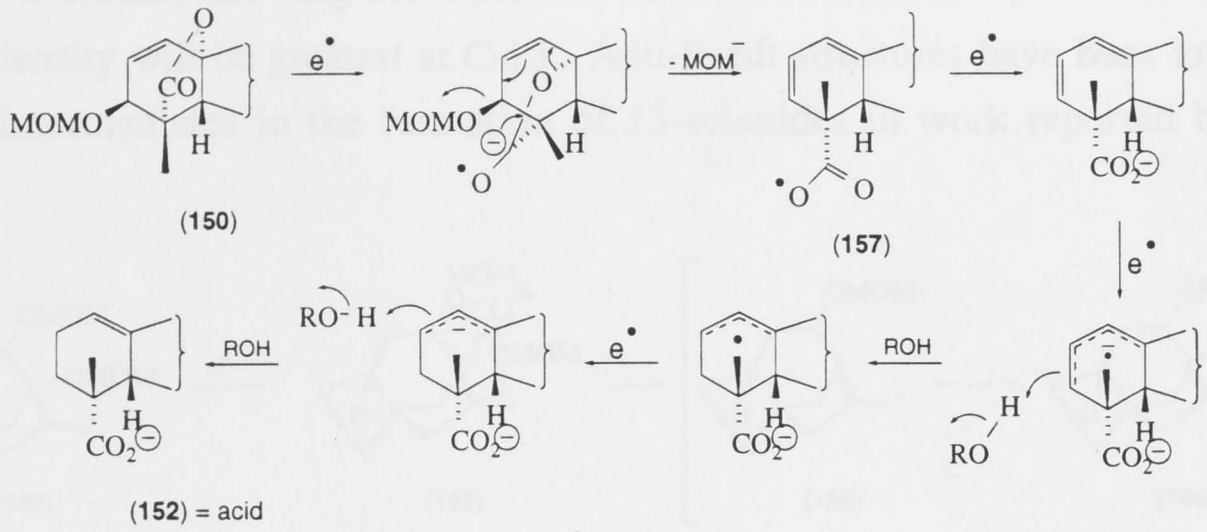
Formulation of a reasonable mechanism to describe the formation of the deoxy compound **135** is not trivial. It has been known for some time that acetoxy groups in the C(13) position can be removed during Birch reductions of cyclopropyl ketones.[101] The mechanism for this process can be understood by transferring an electron from the lithium metal into the π^* molecular orbital of the carbonyl group (Scheme 58). Fragmentation of this species produces a tertiary radical that is reduced by a further electron, and then protonated to form the expected 13-deoxy compound. However, for the deoxygenation of compound **155**, a different deoxygenation mechanism must apply, as the 13-methoxymethoxy group does not possess a sufficiently low lying unoccupied molecular orbital to accommodate an electron in the initial step.



Scheme 58.

* The cyclopentanone function is protected as the enolate.

In Birch reductions of 3-methoxymethyl protected GA_3 **19** and derivatives (eg. compound **150**, Scheme 55, p 48), the methoxymethoxy group is most probably ejected as the anion (Scheme 59).[102] The driving force for the elimination of the methoxymethoxide anion is the formation of the conjugated diene **157**. The resulting diene is then further reduced in the reaction to form the desired acid **152**.



Scheme 59.

In the postulation of a reaction mechanism to explain the formation of the 13-deoxy compound **135**, a number of points must be considered:

(1) 13-deoxygenation products such as **135** have never been observed in other Birch reductions of methoxymethyl protected gibberellins.

(2) no deoxygenation was observed when the reaction was performed on the 12β-methoxymethyl cyclopropyl derivative **179** (as will be discussed in the next section, Scheme 72, p 59).

(3) no trace of the deoxygenation product was found in the reduction of the 12α–methoxymethyl GA_3 derivative **150**, the precursor to the cyclopropyl compound **155**, (exactly the same reaction conditions for both reactions, Scheme 55, p 48).

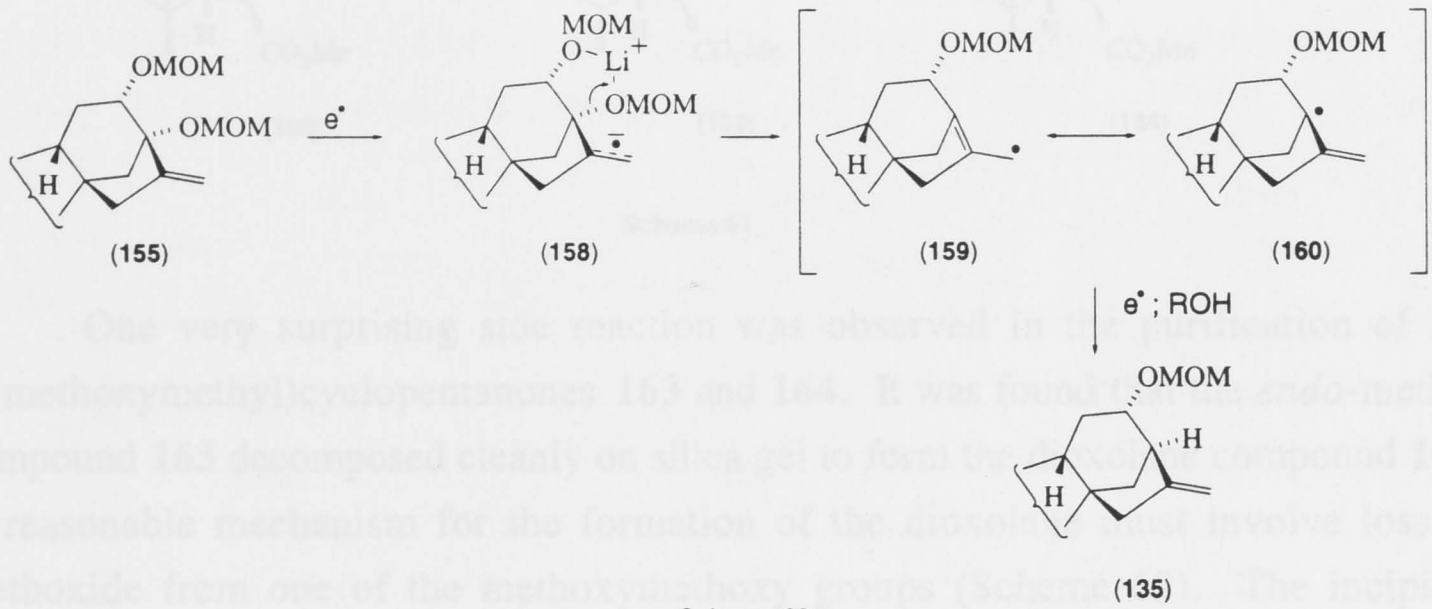
These three points indicate that the precise arrangement of the two methoxymethoxy groups (found in the cyclopropyl compound **155**) is essential for the deoxygenation reaction to occur. The third point illustrates how delicate the balance between deoxygenation or retention must be.

A possible mechanism for the deoxygenation may involve complexation of the lithium cation to the ether oxygens. Complexation of lithium cations by methoxyethoxy groups has been observed by Ronald *et al.*[103] This complexation is optimal for the 12α,13-di(methoxymethyl) compound **155** (in which the two ether groups approach coplanarity), and may assist in the ejection of the 13-methoxymethoxy group.

It is proposed that a solvated electron adds to the terminal olefin function, resulting in ejection of the methoxymethoxide anion, the loss of the anion being assisted by the lithium complexation (**158**). This process forms an allylic radical, represented in

valence bond terms by the two resonance structure **159** and **160**. Addition of a second electron forms the allylic anion which is then protonated, thus forming the deoxy derivative **135**.

The bridgehead olefin **159** clearly violates Bredt's rule,[104] but examination of models indicates a dihedral angle of 65° between the singly occupied orbital at C-13 and the 16,17-π orbital, allowing delocalisation to occur to a limited extent. Clearly, the electron density will be greatest at C-13. Anti-Bredt structures have been invoked as possible intermediates in the formation of 13-selenides in work reported by Willis *et al.*[105]

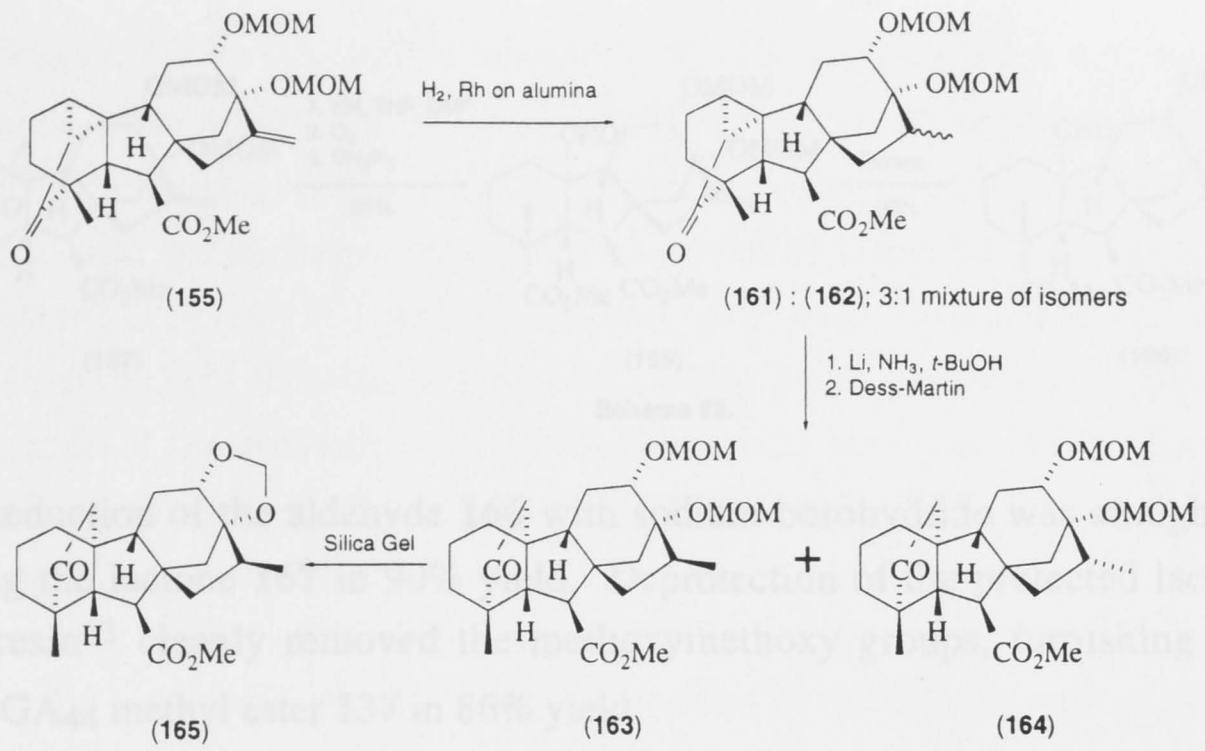


(155) (158) (159) (160) (135)

Scheme 60.

Another, remotely possible mechanism that could explain the deoxygenation of the 13-position involves the addition of the electron into the σ* orbital of the oxygen attached to C(13). This highly excited species would fragment and result in the formation of the tertiary radical **160**. It is assumed that this mechanism would be independent of the 16(17)-olefin. Although this alternative mechanism seemed unlikely, it can not be completely discarded without further evidence.

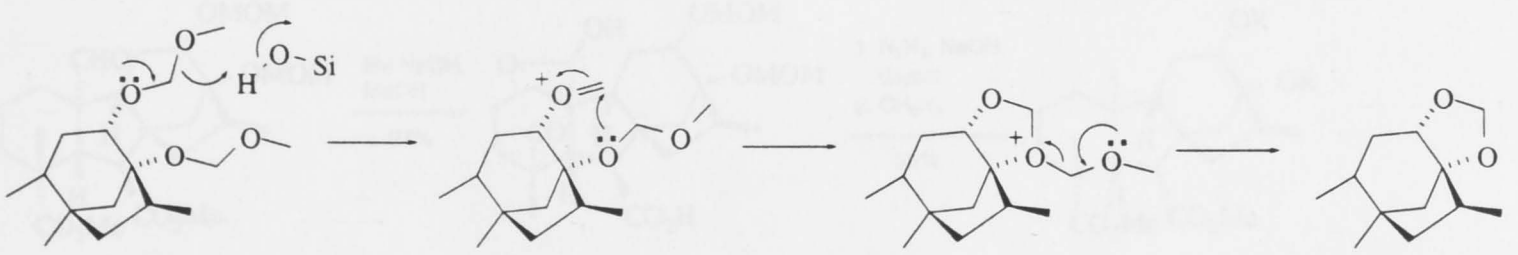
Experimental evidence to prove that the olefin was essential for the deoxygenation could be obtained by subjecting the 16,17-dihydrocyclopropyl ketones **161** & **162** to the conditions of the Birch reduction. This mixture of compounds was easily prepared in quantitative yield by hydrogenation of the cyclopropyl ketone **155** using rhodium on alumina as a catalyst. The reaction provided the desired compounds as a mixture of *endo*-**161** : *exo*-**162** isomers in a ratio of 3:1 (Scheme 61). It was found that the addition of large excesses of lithium metal (followed by oxidation with Dess-Martin reagent in the normal manner) to the dihydro compounds **161** and **162** did not result in any deoxygenation, the only products isolated from the reaction being the expected mixture of di(methoxymethyl)cyclopentanones **163** and **164**. This result provides strong evidence for the involvement of the olefinic bond, and for the validity of the first mechanism presented above (Scheme 60).



Scheme 61.

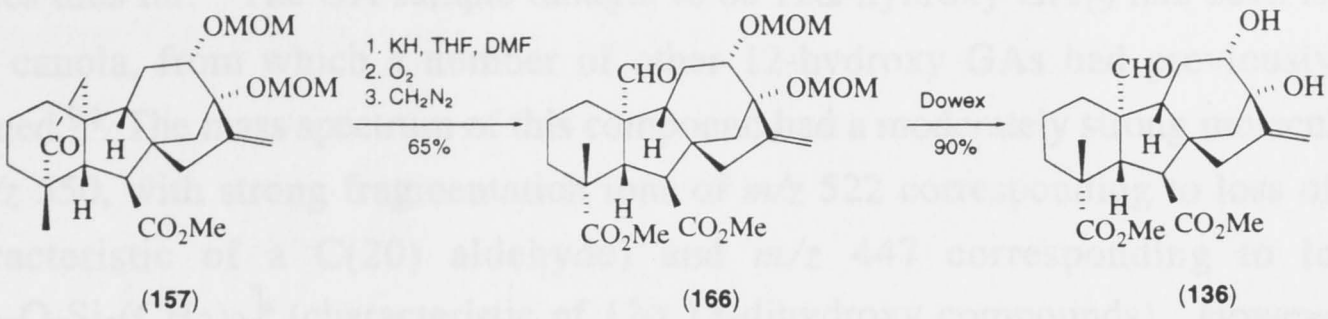
One very surprising side reaction was observed in the purification of the di(methoxymethyl)cyclopentanones **163** and **164**. It was found that the *endo*-methyl compound **163** decomposed cleanly on silica gel to form the dioxolane compound **165**. A reasonable mechanism for the formation of the dioxolane must involve loss of methoxide from one of the methoxymethoxy groups (Scheme 62). The incipient oxonium ion is then attacked by the neighbouring methoxymethoxy group, forming the dioxolane **165**. At present, the only explanation for this strange reactivity is the effect of steric compression from the *endo*-16β-methyl group.

Spectroscopic proof for the structure of **165**, was obtained by a variety of techniques. The mass spectrum had a molecular ion of m/z 374, indicating the loss of 76 mass units ($C_3H_8O_2$) from the parent system which had a molecular ion of m/z 450. Both ^1H and ^{13}C NMR indicated the loss of both methoxymethoxy groups with the appearance of a new methylene group, with signals characteristic of the dioxolane.



Scheme 62.

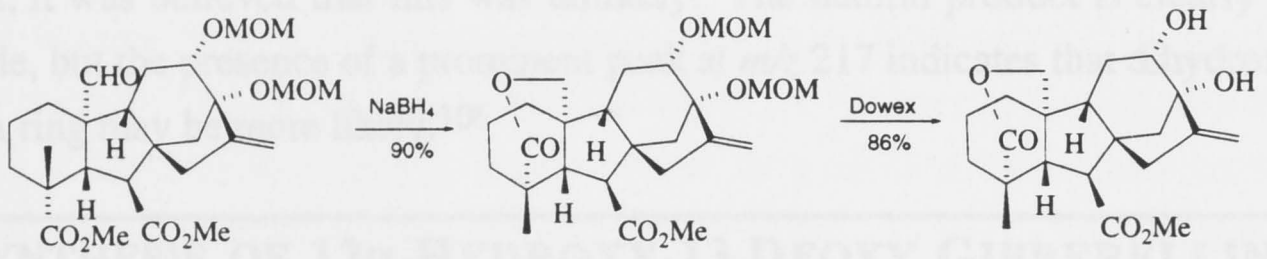
The next step of the synthesis was the oxidative cleavage effected by oxygen gas on the potassium enolate derived from the cyclopentanone **134** (Scheme 63). Treatment of the crude product from the cleavage reaction with diazomethane furnished the desired aldehyde **166** in a rather low 65% yield. Removal of the methoxymethoxy protecting groups was easily performed using Dowex resin in boiling methanol,[63] affording the desired 12α-hydroxy GA_{19} dimethyl ester **136** in 90% yield.



(157) (166) (136)

Scheme 63.

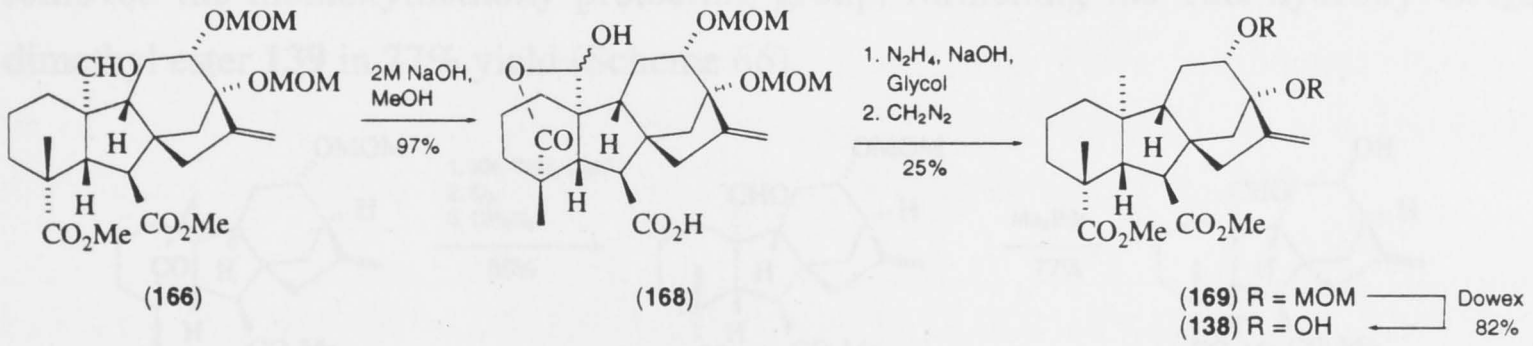
Reduction of the aldehyde **166** with sodium borohydride was straightforward, producing the lactone **167** in 90% yield. Deprotection of the protected lactone with Dowex resin[63] cleanly removed the methoxymethoxy groups, furnishing the 12α-hydroxy GA_{44} methyl ester **137** in 86% yield.



(166) (167) (137)

Scheme 64.

The synthesis of the dimethyl ester of 12α-hydroxy GA_{53} **138** followed the conditions optimised for the synthesis of protected GA_{53} **54** (found on Chapter 2, p 18). Hydrolysis of the methyl esters produced the hydroxy lactone **168** in a virtually quantitative yield. Subjecting the hydroxy lactone **168** to the conditions of the Wolff-Kishner reduction, followed by treatment of the crude residue with diazomethane, then purification on silica gel, afforded the protected 12α-hydroxy GA_{53} **169** in 25% yield. Finally, treatment with Dowex resin in methanol[63] at reflux yielded the desired 12α-hydroxy-GA_{53} dimethyl ester **138** in 82% yield (Scheme 65).



(166) (168)

Scheme 65

Samples of each of the three dihydroxy GAs **136**, **137** and **138** were treated with *bis*-(trimethylsilyl)trifluoroacetamide to form the trimethylsilyl derivatives. These compounds were then subjected to GCMS analysis. Unfortunately, it was found that all three samples did not correspond to any putative GA samples, isolated from natural

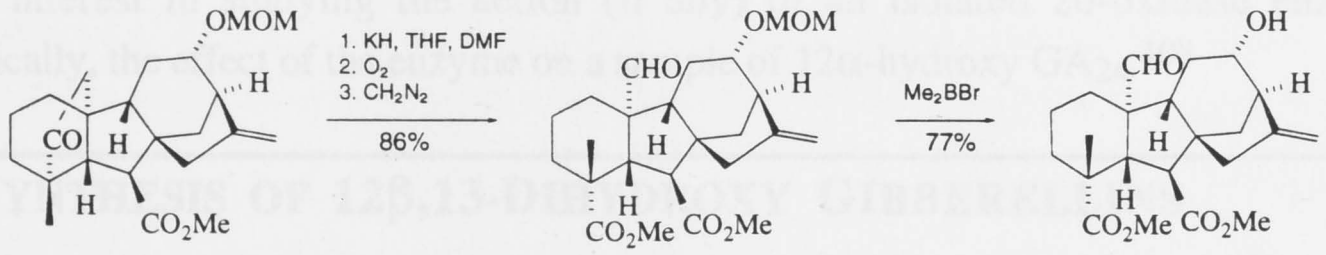
sources thus far.[#] The GA sample thought to be 12α-hydroxy GA_{19} had been isolated from canola, from which a number of other 12-hydroxy GAs had previously been obtained.[94] The mass spectrum of this compound had a moderately strong molecular ion of *m/z* 550, with strong fragmentation ions of *m/z* 522 corresponding to loss of $CO^{\rceil\bullet}$ (characteristic of a C(20) aldehyde) and *m/z* 447 corresponding to loss of $-CH_2-O-Si-(CH_3)_3^{\rceil\bullet}$ (characteristic of 12α,13-dihydroxy compounds). However, the mass spectrum of the synthetic sample **136** displayed a very weak molecular ion of *m/z* 550, with strong fragmentation ions of *m/z* 522 corresponding to loss of $CO^{\rceil\bullet}$, and *m/z* 432 corresponding to loss of $CO^{\rceil\bullet}$ plus $-CH_2-O-Si-(CH_3)_3^{\rceil\bullet}$.

It was possible that the naturally isolated GA could correspond to the 12β-isomer, but due to the large differences in the mass spectra of the 12α-isomer and the natural product, it was believed that this was unlikely. The natural product is clearly a C(20) aldehyde, but the presence of a prominent peak at *m/z* 217 indicates that dihydroxylation in the A ring may be more likely.[106]

5.3 Synthesis of 12α-Hydroxy-13-Deoxy Gibberellins

Starting with the 13-deoxy cyclopentanone **135**, oxidative cleavage effected by oxygen gas on the potassium enolate, followed by treatment with diazomethane, furnished the desired aldehyde **170** in 86% yield.

In the absence of a 13-hydroxy substituent, the 16(17) olefin is extremely reactive towards acid, readily hydrating or migrating into the D-ring. It was for this reason that the use of Dowex resin to remove the 12-methoxymethoxy group would not be suitable. It has been found that the Lewis acid, dimethylboron bromide[107] efficiently deprotects methoxymethyl ethers without rearrangement of the double bond.[101] Thus, treatment of the aldehyde **170** with dimethylboron bromide in dry dichloromethane at -78°C cleanly removed the methoxymethoxy protecting group, furnishing the 12α-hydroxy GA_{24} dimethyl ester **139** in 77% yield (Scheme 66).



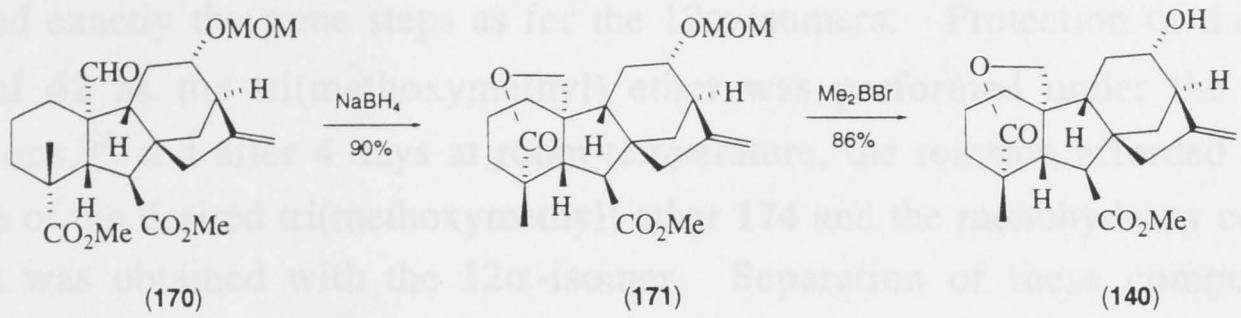
(135) **(170)** **(139)**

Scheme 66.

Reduction of the aldehyde **170** with sodium borohydride produced the lactone **171** in 79% yield (Scheme 67). This compound was also cleanly deprotected by

[#] The author gratefully acknowledges the formation of the TMS derivatives, followed by GCMS analysis of the three compounds **136**, **137** and **138**, by Dr. Paul Gaskin and Jacqui Whalley.

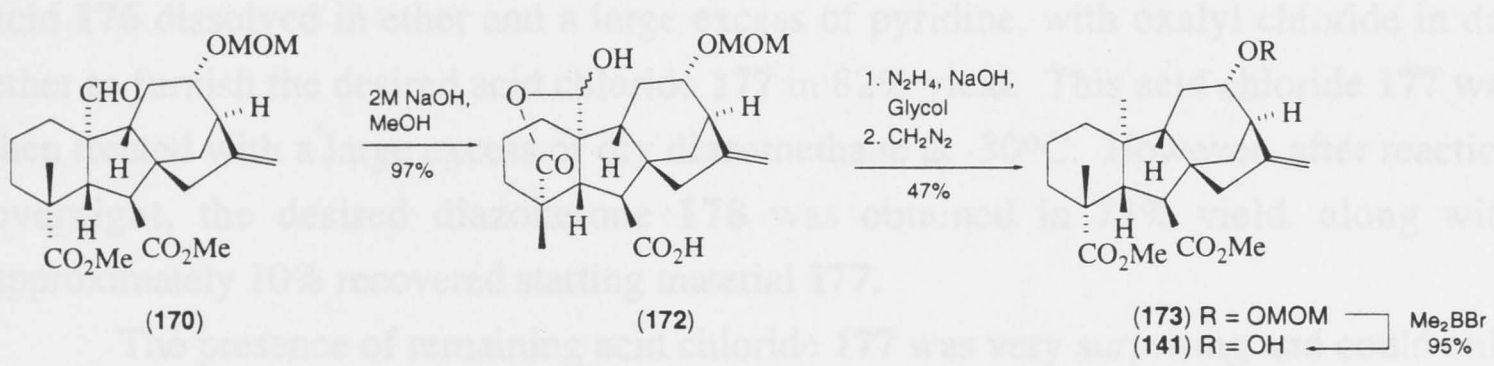
treatment with dimethylboron bromide in dry dichloromethane at -78°C, furnishing the 12α-hydroxy GA_{15} methyl ester **140** in 95% yield.



(170) (171) (140)

Scheme 67.

The synthesis of the dimethyl ester of 12α-hydroxy GA_{12} **141** once again followed the conditions optimised for the synthesis of protected GA_{53} **54** (found in Chap. 2, p 18). Hydrolysis of the methyl esters of compound **170** produced the hydroxy lactone **172** in a virtually quantitative yield (Scheme 68). Subjecting the hydroxy lactone **172** to the conditions of the Wolff-Kishner reduction, followed by treatment of the crude residue with diazomethane, then purification on silica gel afforded the protected 12α-hydroxy GA_{12} **173** in 47% yield. Finally, deprotection of the methoxymethoxy ether group with dimethylboron bromide at -78°C, yielded the desired 12α-hydroxy-GA_{12} dimethyl ester **141** in a high 95% yield.



(170) (172)

Scheme 68.

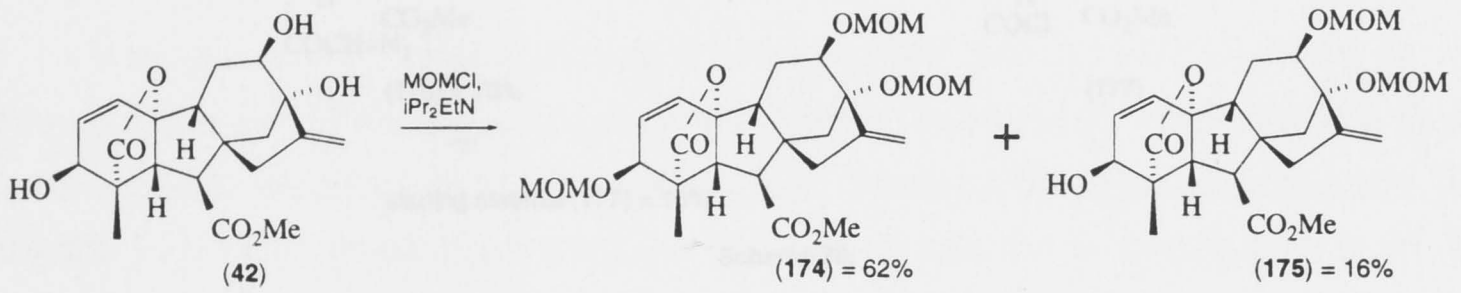
With the synthesis of all three compounds **139**, **140** and **141** successfully completed, GCMS analysis was undertaken of the trimethylsilyl derivatives.* However, comparisons with putative gibberellins have yet to be made. These compounds will also be of interest in studying the action (if any) of an isolated 20-oxidase enzyme, specifically, the effect of the enzyme on a sample of 12α-hydroxy GA_{24}.[108]

5.4 Synthesis of 12β,13-Dihydroxy Gibberellins

Although an easier pathway to obtain the 12β-isomers was *via* an oxidation/reduction cycle of the 12α-isomers (as discussed on p 44 - 45), it was of theoretical interest to see if the 12β,13-dimethoxymethyl cyclopropyl compound **179** (Scheme 71, p 58) underwent the same 13-deoxygenation as found for the

* The author gratefully acknowledges the formation of the TMS derivatives, followed by GCMS analysis of the three compounds **139**, **140** and **141**, by Dr. Paul Gaskin and Jacqui Whalley.

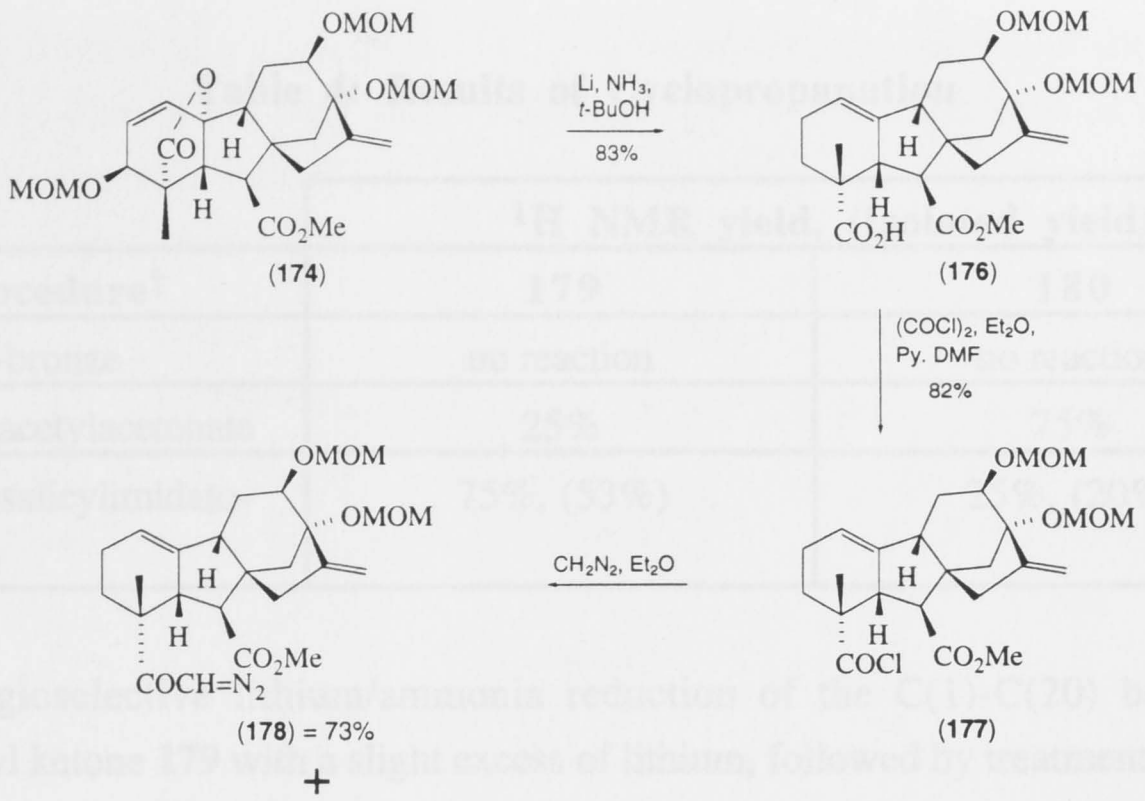
12α-derivative **155** (Scheme 57, p 50). Thus, starting with the 12β-hydroxy GA_3 methyl ester **42**, the synthesis of the 12β-hydroxy compounds **142**, **143** and **144** followed exactly the same steps as for the 12α-isomers. Protection of the starting material **42** as the tri(methoxymethyl) ether was performed under the standard conditions,[64] and after 4 days at room temperature, the reaction afforded a similar mixture of the desired tri(methoxymethyl) ether **174** and the monohydroxy compound **175** as was obtained with the 12α-isomer. Separation of these compounds by chromatography was straightforward and afforded pure samples of compound **174** and **175** in 62% and 16% yield respectively.



Scheme 69.

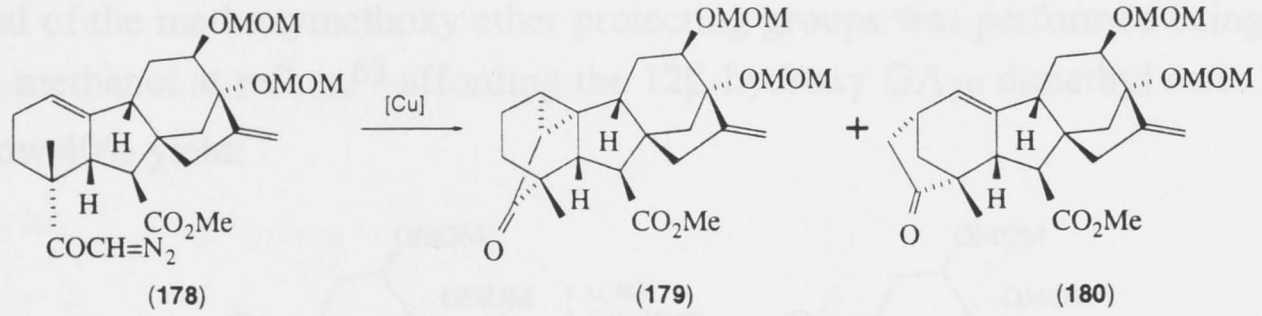
Dissolving metal reduction using lithium/ammonia proceeded smoothly to produce the acid **176** in 83% yield (Scheme 70). This was followed by treatment of the acid **176** dissolved in ether and a large excess of pyridine, with oxalyl chloride in dry ether to furnish the desired acid chloride **177** in 82% yield. This acid chloride **177** was then treated with a large excess of dry diazomethane at -30°C. However, after reaction overnight, the desired diazoketone **178** was obtained in 73% yield, along with approximately 10% recovered starting material **177**.

The presence of remaining acid chloride **177** was very surprising and could only be rationalised by assuming that the overall conformations of the 12β- and 12α-isomers were different. By examination of models, it can easily be seen that when the C-ring adopts the boat conformation, which is favoured in most gibberellin derivatives,[109] the 12β–methoxymethoxy group is axially disposed. However, it is believed that the C-ring may adopt a conformation that allows the 12β-methoxymethoxy group to become more equatorial like. This distortion of the GA skeleton could lead to steric interactions on the α-face of the molecule which results in the observed changes in reactivity.



Scheme 70.

As before, the three "standard" copper catalysts were tried, in order to see which would give the optimal yield of the cyclopropyl ketone (Scheme 71). The ratios of the crude products were determined by ^{1}H NMR spectroscopy and the results from these experiments are presented in Table 4.



Scheme 71.

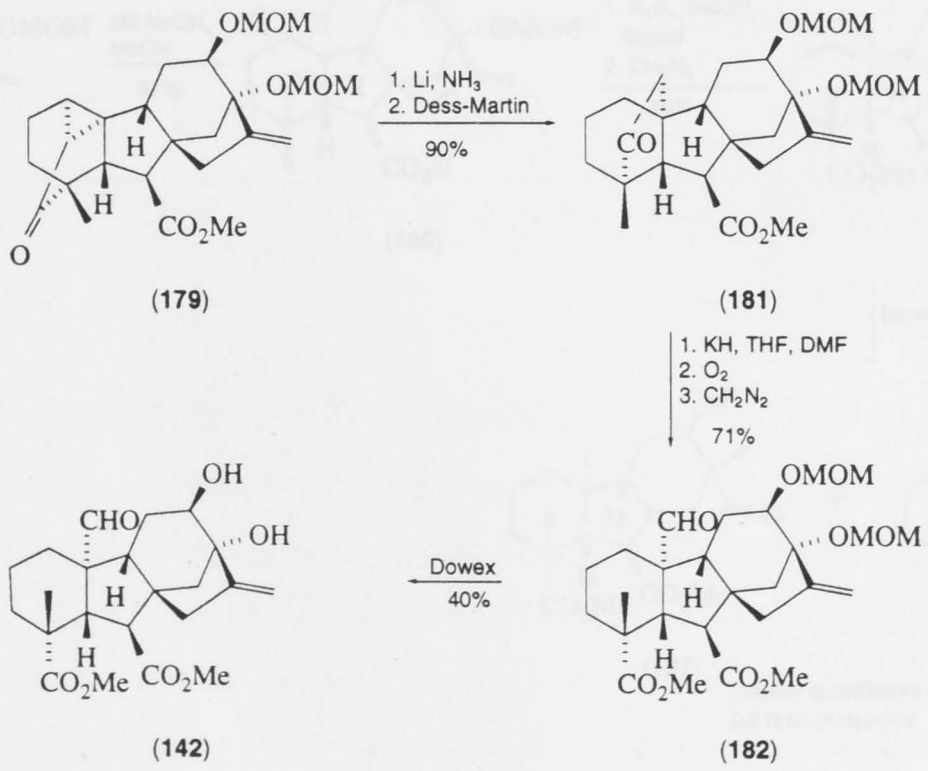
In the cyclopropanation reaction, similar selectivities as with the 12α-hydroxy diazoketone **154** (Table 3, p 49) were expected. However, with the copper-bronze catalyst, no reaction was observed at all, even after reflux for several hours. This result is consistent with the reduced reactivity of the C(19) acyl group of the 12β isomer **177** (compared to the 12α isomer **153**, p 48) in the formation of the diazoketone **178**. Copper acetylacetonate was once again an inferior catalyst for cyclopropanation, favouring the formation of the C-H insertion product **180**. However, the t-butylsalicylimidato cuprate catalyst produced the desired cyclopropyl ketone **179** in a reasonable yield.

Table 4: Results of Cyclopropanation

	^{1}H NMR yield, (Isolated yield)	
Procedure†	**179**	**180**
A: copper-bronze	no reaction	no reaction
B: copper acetylacetonate	25%	75%
C: t-butyl-salicylimidato-cuprate	75%, (53%)	25%, (20%)

Regioselective lithium/ammonia reduction of the C(1)-C(20) bond in the cyclopropyl ketone **179** with a slight excess of lithium, followed by treatment with Dess-Martin reagent, produced only the expected di(methoxymethoxy)cyclopentanone **181** (Scheme 72). This result confirmed the postulation that the α–configuration of the 12-methoxymethoxy group is essential for the deoxygenation reaction to occur (Scheme 57, p 59).

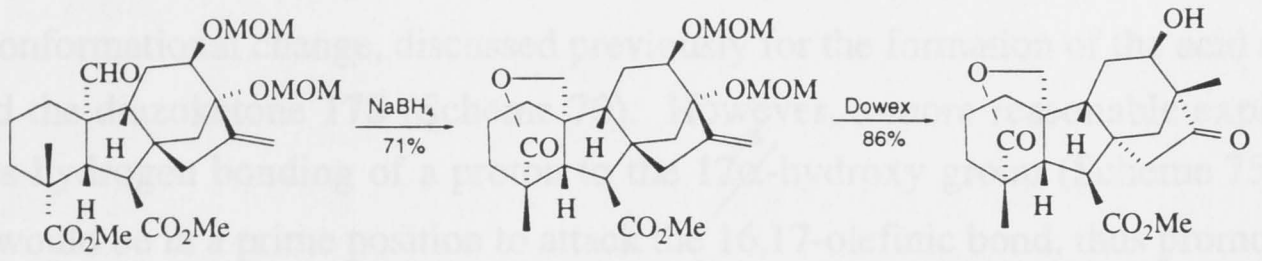
The cyclopentanone **181** was subjected to the conditions of the oxidative cleavage of the C(19)-C(20) bond. This was followed by treatment of the crude reaction product with diazomethane, furnishing the desired aldehyde **182** in 71% yield (Scheme 72). Removal of the methoxymethoxy ether protecting groups was performed using Dowex resin in methanol at reflux,[63] affording the 12β-hydroxy GA_{19} dimethyl ester **142** in a rather low 40% yield.



Scheme 72.

Reduction of the aldehyde **182** with sodium borohydride was straightforward, producing the lactone **183** in 71% yield. However, attempted removal of the methoxymethyl groups using Dowex resin resulted in a Wagner-Meerwein rearrangement

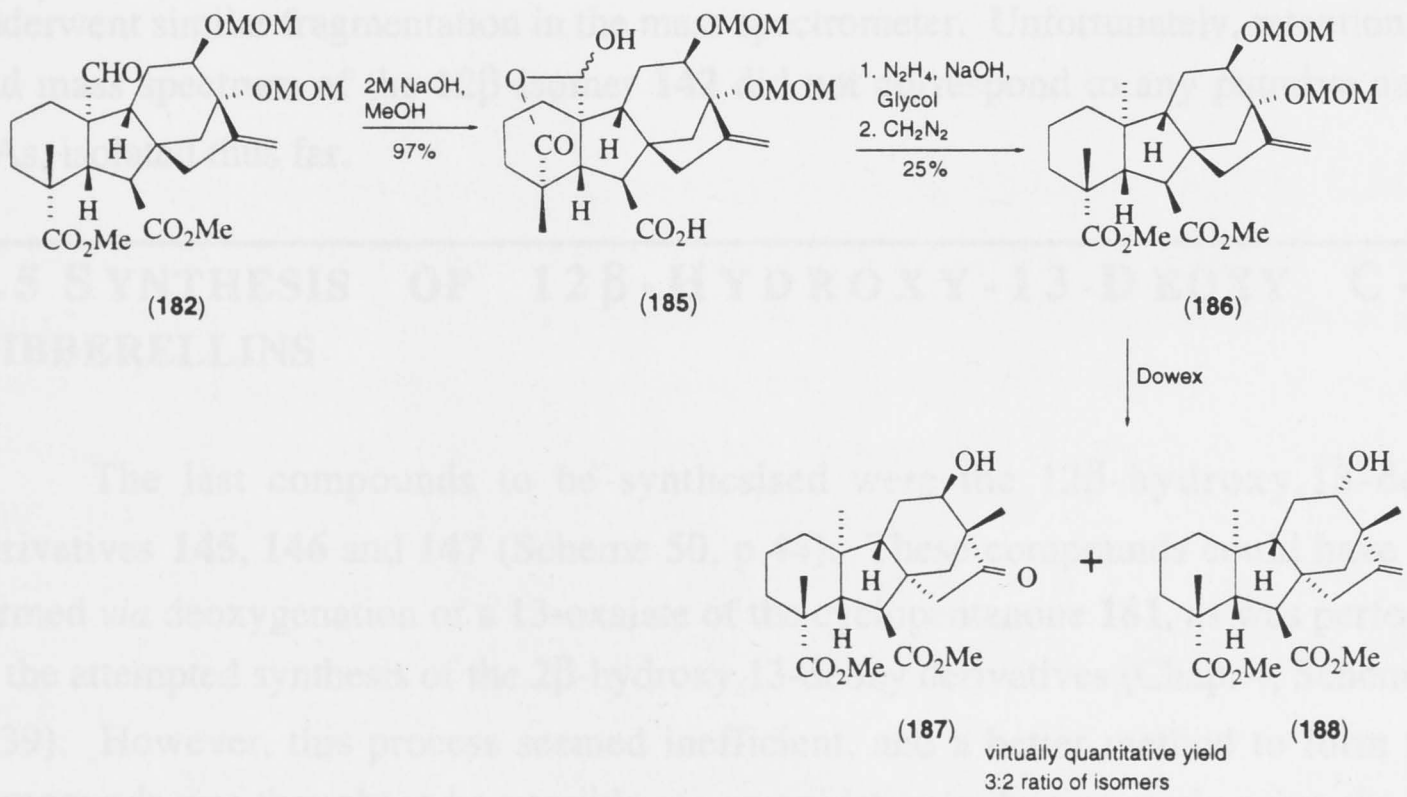
of the C-D rings of the gibberellin.[110] This rearrangement furnished the undesired 13-methyl-16-one **184** in 86% yield. Although the ^{1}H NMR spectrum of **184** clearly displayed the expected signals for the C(20)-methylene group, the characteristic signals for the olefinic region were lost, with the appearance of a new methyl signal at 1.14 ppm.



(182) (183) (184)

Scheme 73

Finally, the attempted synthesis of the dimethyl ester of 12β-hydroxy GA_{53} **144** was conducted following the conditions optimised for the synthesis of protected GA_{53} **54** (found in Chap. 2, p 18). Hydrolysis of the methyl esters in compound **182** produced the diacid aldehyde **185** in virtually quantitative yield (Scheme 74). Subjection of the diacid **185** to the conditions of the Wolff-Kishner reduction, followed by treatment of the crude residue with diazomethane, then purification on silica gel, afforded the protected 12β-hydroxy GA_{53} **186** in 25% yield. Once again, treatment with Dowex resin in methanol under reflux[63] resulted in Wagner-Meerwein rearrangement of the C-D rings.[110] Moreover, a mixture of two isomers was obtained, the 12β-hydroxy compound **187** and the 12α-epimer **188**.



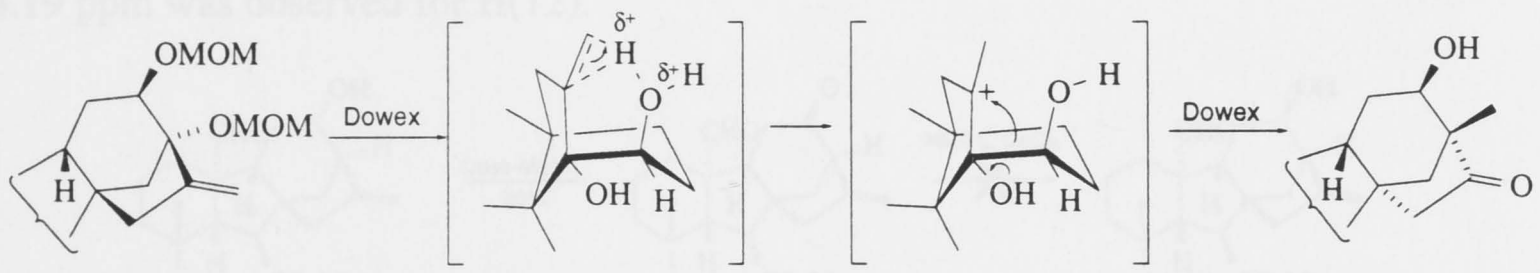
(182) (185) (186) (187) (188)

Scheme 74.

The compounds were separated by flash chromatography and structures were assigned based on their ^{1}H NMR spectra. Both compounds had similar ^{1}H NMR spectra, with the loss of the olefinic signals and the appearance of the C(13) methyl group at 1.07 ppm and 1.12 ppm respectively. The latter compound **188** had a significantly

broader signal for the H(12) multiplet at 3.54 ppm and therefore was tentatively assigned as the α-isomer, due to the larger coupling expected for the axial proton. This 12α-isomer **188** is presumably formed *via* a retro-Aldol type of reaction of the 12β-compound **187**.

The reason as to why the 12β-isomers readily undergo rearrangement may be due to the conformational change, discussed previously for the formation of the acid chloride **177** and the diazoketone **178** (Scheme 70). However, a more reasonable explanation involves hydrogen bonding of a proton to the 12α-hydroxy group (Scheme 75). This proton would be in a prime position to attack the 16,17-olefinic bond, thus promoting the rearrangement of these compounds.



Scheme 75

Formation of the trimethylsilyl derivative of 12β-hydroxy GA_{19} **142**, was followed by GCMS analysis.# The mass spectrum of this compound correlated fairly well with that obtained from the 12α-isomer **136**, showing that the two compounds underwent similar fragmentation in the mass spectrometer. Unfortunately, retention time and mass spectrum of the 12β-isomer **142** did not correspond to any putative natural GAs, isolated thus far.

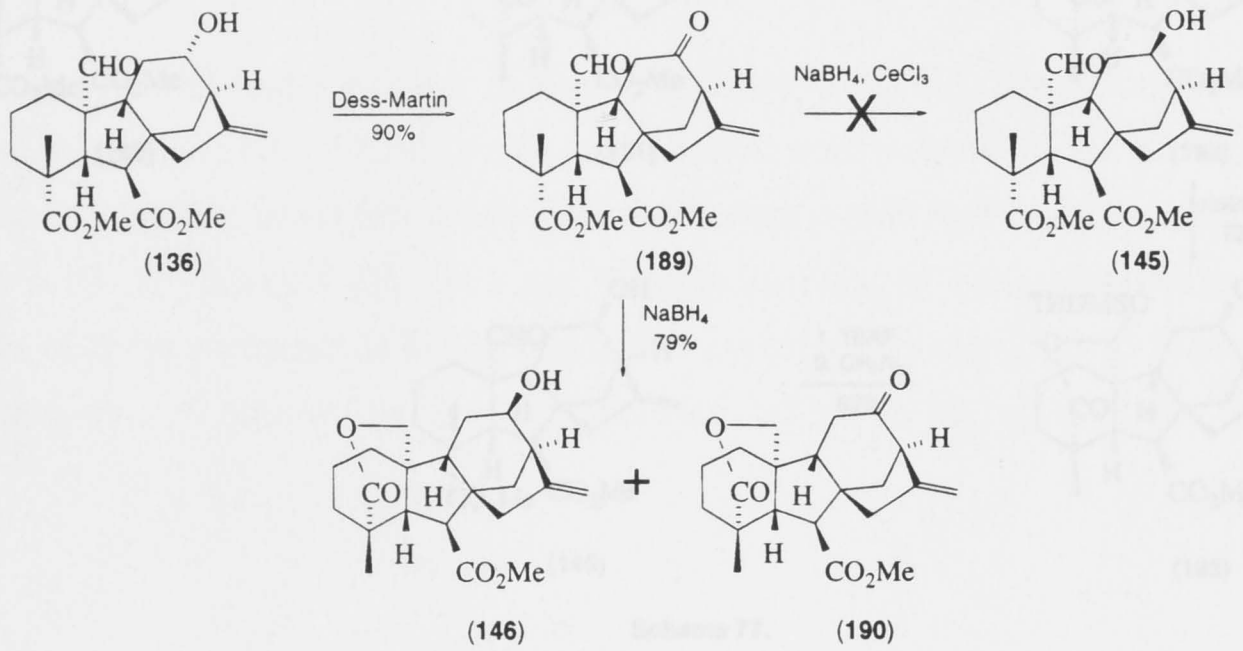
5.5 Synthesis of 12β-Hydroxy-13-Deoxy C-20 Gibberellins

The last compounds to be synthesised were the 12β-hydroxy,13-deoxy derivatives **145**, **146** and **147** (Scheme 50, p 44). These compounds could have been formed *via* deoxygenation of a 13-oxalate of the cyclopentanone **181**, as was performed in the attempted synthesis of the 2β-hydroxy,13-deoxy derivatives (Chap. 4, Scheme 42, p 39). However, this process seemed inefficient, and a better method to form these compounds was thought to be possible *via* an oxidation/reduction cycle using the 12α-derivatives.

The author gratefully acknowledges the formation of the TMS derivatives, followed by GCMS analysis of **142** by Dr. Paul Gaskin and Jacqui Whalley.

Oxidation of the 12α-hydroxy GA_{24} dimethyl ester **136** with Dess-Martin reagent[60] proceeded smoothly affording the desired 12-ketone **189** in 90% yield (Scheme 76). Reduction of this compound with a slight excess of sodium borohydride afforded a mixture of the first target compound, 12β-hydroxy GA_{15} methyl ester **146** and the 12-ketolactone **190**.

Proof for the structure of compound **146** was obtained by comparison of the ^1H NMR spectra of this and the 12α-isomer. The ^1H NMR of the lactone **146** had characteristic signals for the C(20) methylene with a doublet at 4.07 that had a geminal coupling of 12.1 Hz and a doublet of doublets at 4.34 ppm with a geminal coupling of 12.1 Hz plus a smaller W coupling of 2.4 Hz to the 1β-proton. In addition, a multiplet at 4.19 ppm was observed for H(12).



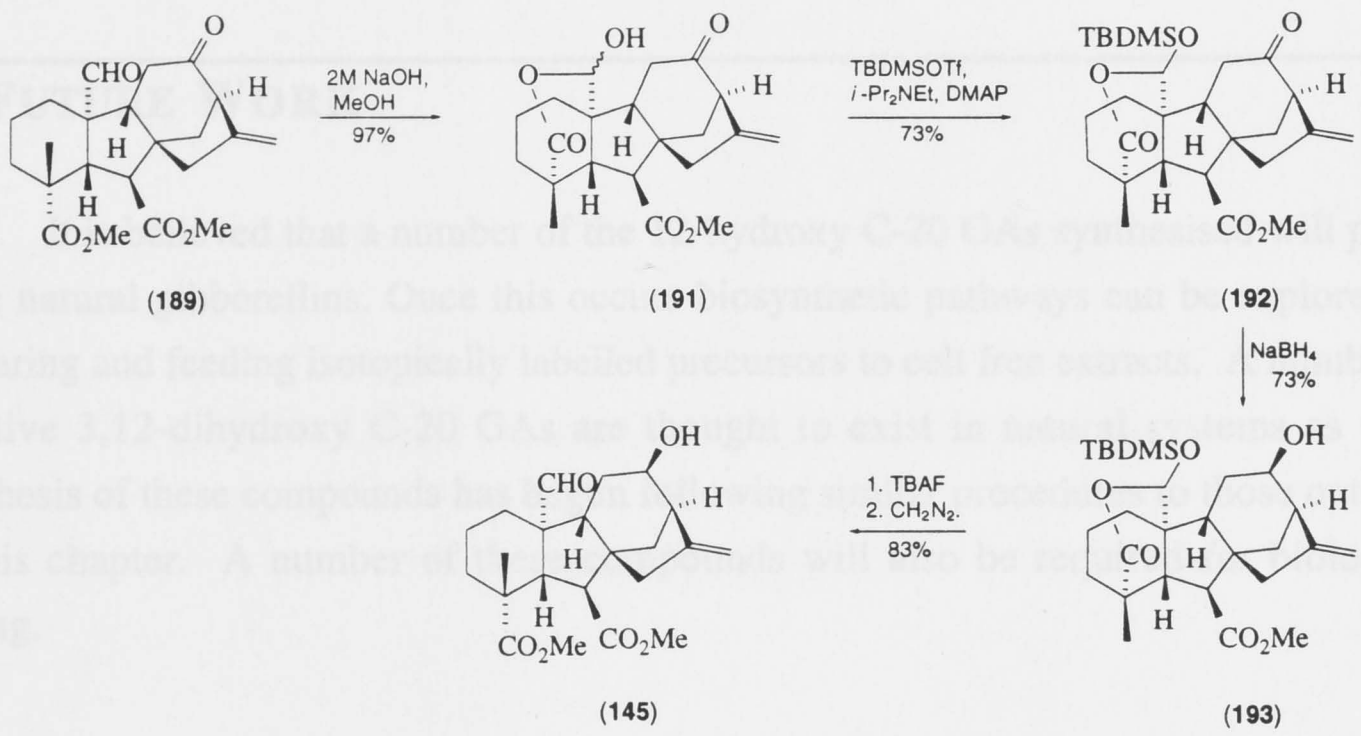
Scheme 76.

It was hoped that chemoselective reduction of the 12-ketone function would be possible by selective formation of the geminate diol of the aldehyde function by treatment with cerium trichloride, in a mixture of ethanol/water.[111] This hydration has effectively protected the aldehyde group in simpler substrates, thereby allowing selective reduction of the ketone *in situ* with sodium borohydride. It was believed that this methodology might provide quick access to the desired 12β-hydroxy GA_{24} dimethyl ester **145**. Unfortunately, in the presence of cerium no reaction occurred, and other attempts at selective reduction (using low temperature reduction with sodium borohydride, as well as zinc borohydride) were also unsuccessful.

The failure to reduce the ketone group selectively in the presence of the aldehyde function meant that suitable protection of the aldehyde was required. Protection of the C(20) aldehyde had previously been achieved *via* the formation of the methyl ether of the C(19),C(20) lactol.[112] However, deprotection of these ethers requires acidic conditions, this being incompatible with the sensitive 16-methylene group.[113] It was believed that

formation of the TBDMS ether would be relatively straightforward,[114] with the removal of the group being achieved under mild, nonacidic conditions.[115]

The synthesis began with the selective hydrolysis of the C(19) methyl ester in compound **189**, to form the lactol **191** in virtually quantitative yield (Scheme 77). Protection of the lactol with *t*-butyldimethylsilyl triflate (TBDMSOTf) proceeded smoothly, furnishing the silylether **192**, which was reduced with sodium borohydride to afford the alcohol **193**. Deprotection with TBAF in THF/water, followed by treatment with diazomethane, furnished the desired 12β-hydroxy GA_{24} dimethyl ester **145** in 43% overall yield.

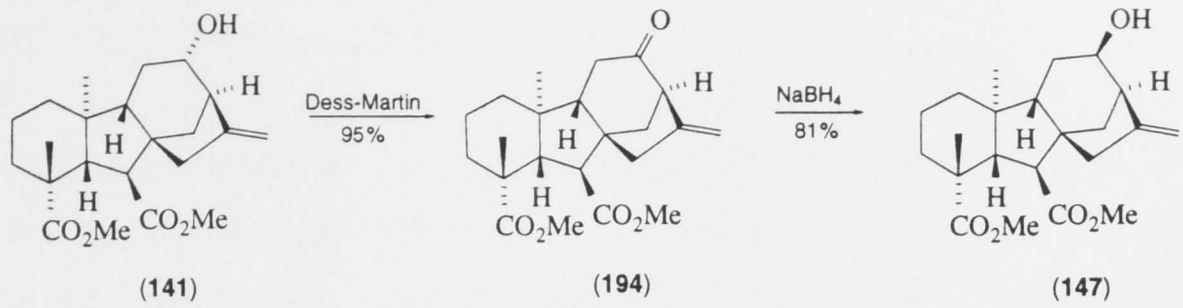


(189) (191) (192) (193) (145)

Scheme 77.

The spectra of both compound **145** and the 12α-isomer **139** were very similar, and observation of the signals for H(12) in both compounds was not possible, due to overlapping with the signals from the methyl esters. Determination of structure came from the examination of the signal for H(13). The H(13) signal for compound **139** is a distinct doublet with a coupling constant of 4.5 Hz between H(12) and H(13) clearly indicating the quasi-equatorial nature of the H(12) proton, whereas the signal for H(13) in **145** is broad with no resolved coupling to H(12). This result is consistent with H(12) being quasi-axial in the latter isomer.

Finally, the C(20) methyl derivative **147** was cleanly obtained in the same manner as for the lactone **146**. Oxidation of the 12α-hydroxy GA_{12} dimethyl ester **141** to the 12-ketone **194** followed by reduction of the ketone with sodium borohydride, furnished the desired 12β-hydroxy GA_{12} dimethyl ester **147** in 77% yield over the two steps.



(141) (194) (147)

Scheme 78.

GCMS analysis of the trimethylsilyl derivatives of each of the three 12β-hydroxy samples **145**, **146** and **147** has yet to be performed, but it is expected that all three compounds will correspond to natural gibberellins.

5.6 FUTURE WORK

It is believed that a number of the 12-hydroxy C-20 GAs synthesised will prove to be natural gibberellins. Once this occurs biosynthetic pathways can be explored by preparing and feeding isotopically labelled precursors to cell free extracts. A number of putative 3,12-dihydroxy C-20 GAs are thought to exist in natural systems as well. Synthesis of these compounds has begun following similar procedures to those outlined in this chapter. A number of these compounds will also be required for biological testing.

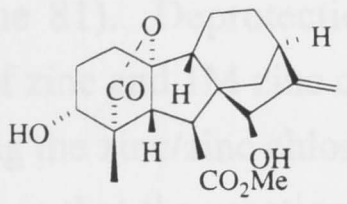
Chapter Six

The Synthesis of C-19 15β-Hydroxy Gibberellins:

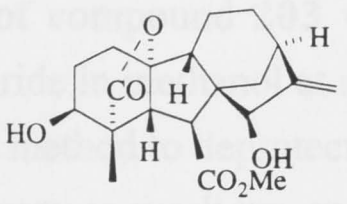
3-*epi*-GA_{63}

6.1 INTRODUCTION

As practice for the synthesis of the three 15β-hydroxy C-20 GAs described in Chap. 3, (p 22), another 15β-hydroxy GA, 3-*epi*-GA_{63} methyl ester **195** was required to confirm the identity of a putative gibberellin. This new GA had been found by Yamane and coworkers in *Anemia phyllitidis.*[116] The synthesis of this compound was straightforward based on the work done by MacMillan *et al.* in their synthesis of GA_{63} methyl ester **196.**[58]



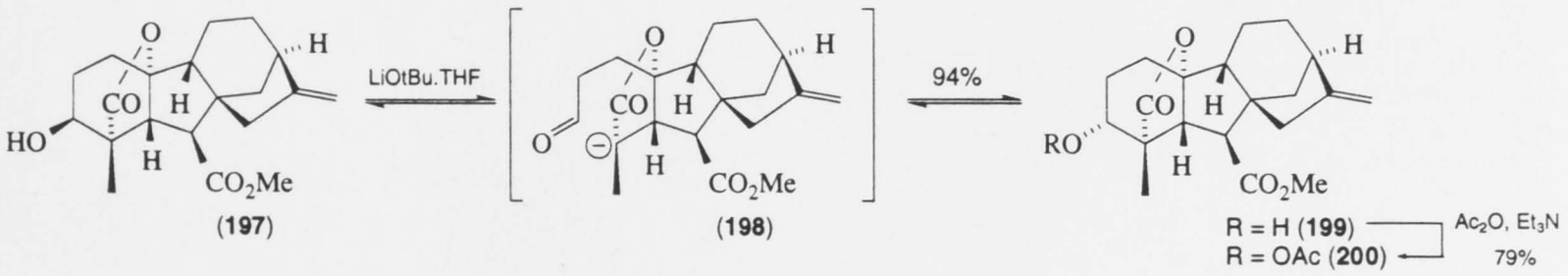
(195)



(196)

6.2 SYNTHESIS OF 3-*epi*-GA_{63}

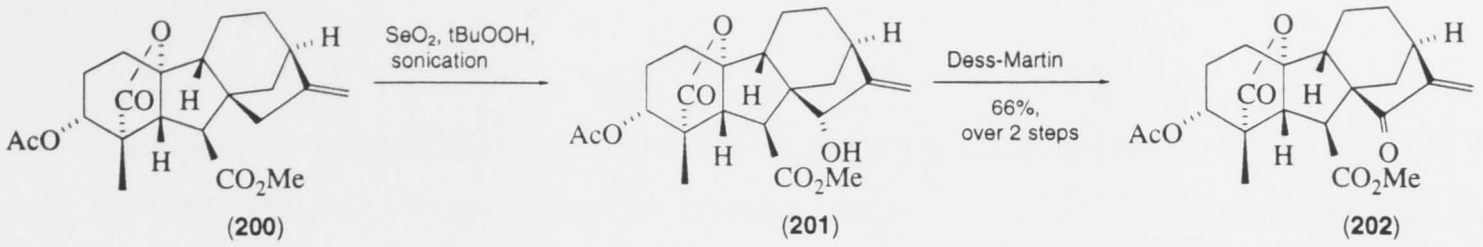
The synthesis of 3-*epi*-GA_{63} **195** began with the epimerisation of the 3β-hydroxy group of GA_4 methyl ester **197** to the thermodynamically favoured equatorial 3α–hydroxy compound **199**. This was achieved by a retro-aldol reaction, whereby the gibberellin, in a solution of lithium *t*-butoxide in THF, equilibrates between the starting material **197**, the open chain intermediate **198** and the final compound **199** (Scheme 79), the equilibrium being driven to the right by the formation of the thermodynamically more stable equatorial hydroxyl derivative.[117] After 48 hours, the desired 3α-hydroxy GA_4 methyl ester **199** was isolated in 94% yield. The material was then protected as the 3α-acetate **200**.



(197) (198)

Scheme 79.

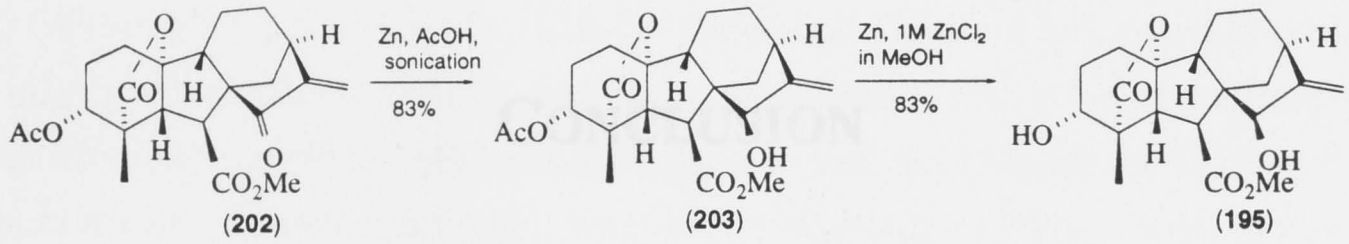
Allylic oxidation of the 3α-acetate **200** with selenium dioxide and *t*-butylhydroperoxide[59] afforded the 15α-hydroxy derivative **201** (Scheme 80). As the 15α-hydroxy group can lactonize with the 7-methyl ester, the material was taken without purification and oxidised to the enone **202** using the Dess-Martin reagent.[60] The enone was isolated cleanly in 66% yield over the two steps .



(200) (201) (202)

Scheme 80.

Reduction of the enone **202** to the 15β-hydroxy compound **203** was accomplished using the standard conditions as applied by MacMillan.[58] The use of zinc and acetic acid under sonication cleanly afforded the desired 15β-hydroxy derivative **203** in 83% yield (Scheme 81). Deprotection of compound **203** was accomplished by heating in a mixture of zinc and 1M zinc chloride in methanol at reflux (Scheme 81).[118] The advantage of using the zinc/zinc chloride method to deprotect the acetate over more conventional methods is that the reaction is easy to work up, and often the material is obtained in better yields, as chromatography is not essential.



(202) (203) (195)

Scheme 81.

The synthesis of epi-GA_{63} methyl ester **195** was completed in 34% overall yield. After derivatisation as the trimethylsilyl derivative, its identity as a new gibberellin was confirmed by GCMS. The remaining material was deprotected and bioassays were performed to check the biological activity of the gibberellin on *Anemia phyllitidis*. Results from these experiments are found in the report by Yamane and coworkers.[116]

Chapter Seven

Conclusion

7 CONCLUSION

The initial aim of this project was to develop a general method for the production of C(20)-methyl GAs. The realisation of this goal *via* a Wolff-Kishner reduction has opened up the possibility of obtaining all four oxidation states of the C-20 GAs from a common intermediate. This methodology provides a reliable route to GA_{53}, thereby allowing the production of reasonable quantities of deprotected material for biological assays, as well as the formation of isotopically labelled derivatives.

The next goal was to extend the C-20 GA methodology to obtain further hydroxylation patterns, in particular 2,12, 12,13 and 13,15. These derivatives were required in order to confirm tentative assignments of a number of putative GAs. This work resulted in the successful synthesis of seventeen target compounds. Confirmation of structures for seven new C-20 gibberellins, from the targets synthesised, have already been made, with the prospect of a number of others still to come.

Although a number of the 12α,13-dihydroxy GAs did not correspond to any presently isolated natural GAs (especially from Canola), they may be isolated in the future. Moreover, with the successful completion of all the 12-hydroxy C-20 variants, a complete set of reference spectra has been obtained, thereby making future assignments of new GAs more straightforward. It is a simple fact that, by eliminating possibilities, better estimates can be made as to what the correct structure of the unknown may be. A good analogy for this process is a jigsaw puzzle, the more pieces that are put in place, the easier it is to put new pieces into the correct place.

The syntheses presented here consolidate and improve a wide range of synthetic methodology. Many of the steps becoming almost routine, thereby strengthening confidence in the reliability of the methodology, such that it can be successfully extended to future targets.

This work has also discovered some fascinating and intriguing chemistry with numerous examples of the effects of subtle structural changes on the reactivity of functional groups, some of the more interesting examples of this being:

(1) The lack of reactivity of the 12β-isomers, such as the acid chloride **177** and diazoketone **178**, compared to the 12α-isomers (Chap. 5, p 59).

(2) The propensity of the 12β-hydroxy compounds to rearrange, as displayed in the attempted deprotection of the lactone **183**, and the C(20)-methyl compound **186** (Chap. 5, p 60 - 61).

(3) The isolation of the unusual enol ether **107**, from the cyclopropanation reaction with the 2β-methoxymethyl diazoketone **103**. Compounds like **107** have never been observed before in cyclopropanation reactions, and may provide important insight into the mechanism of C-H insertion reactions (Chap. 4, p 31 - 32).

(4) The varitation in the outcome of copper catalysed diazoketone decompositions. Without further experimentation it is difficult to rationalise these variations in catalyst and substrate. Therefore, with the time available no rationalisations of this were undertaken, and an empirical approach to the yields was taken.

(5) The deoxygenation of the 13-methoxymethyl group in the cyclopropyl ketone **155**. This result was most surprising, but allowed much more direct access to the 13-deoxy series (Chap. 5, p 49 - 51).

This selection of examples above show how the high density of functionality on the highly strained GA skeleton can lead to very complex chemistry that is both useful and intriguing.

Future work is aimed at completing the synthesis of the 2β-hydroxy C-20 compounds **85**, **86** and **87** (attempted in Chap 4, p 38 - 41). Work is also presently underway in the synthesis toward the 3,12,13-trihydroxy and 3,12-dihydroxy C-20 derivatives. All of these compounds are once again required for the ongoing process of confirming the structures of new putative GAs.

With the technical ability to synthesise many of the structural isomers of GAs, combined with the biological work being done with immunochemistry and molecular biology, it is believed that a greater understanding of the intricate nature of gibberellin biosynthesis and biochemistry is achievable. Studying the complex "gibberellin jigsaw" is not only an intellectually stimulating challenge, but can provide vital information for the specific modification of plant growth and development that could ultimately be exploited commercially.

CHAPTER EIGHT

EXPERIMENTAL

8.1 General Experimental

Melting points were recorded on a Reichert hot-stage and are uncorrected.
Microanalysis were carried out by the Australian National Unversity Analytical Services Unit, Canberra. C,H,N analyses were measured on a Carlo Erba EA 1106 CHN-O machine.
Low resolution EI mass spectra (70 eV) were recorded on a VG Micromass 7070F double focussing mass spectrometer. The molecular ion (M^+), if present, significantly high mass ions and the more intense low mass ions are reported. Data are presented in the following order: *m/z* value; relative intensity as a percentage of the base peak. All mass spectra recorded as EI unless otherwise stated. High resolution mass spectra (exact mass) were also determined on the 7070F machine, by peak matching.

Infrared spectra (υ_{max}) were recorded on a Perkin-Elmer 683 Infrared spectrophotometer in 0.25 mm NaCl solution cells using deuterochloroform. The frequency of the absorbance (cm^{-1}) were directly referenced to the charateristic peak at 1601 cm^{-1} for polystyrene film.

^1H NMR spectra were recorded on the following instruments: Varian Gemini 300 at 300 MHz, Varian VXR300 at 300 MHZ and Varian VXR500 at 500 MZ. ^{13}C NMR spectra were recorded on the following instruments: Varian Gemini 300 at 75.5 MHz and Varian VXR300 at 75.5 MHz. Chemical shifts are reported as values in parts per million (δ ppm). For proton spectra recorded in chloroform, the residual peak of $C\underline{H}Cl_3$ was used as the internal reference (7.26 ppm) while the central peak of $CDCl_3$ (77.0 ppm) was used as the reference for carbon spectra. Proton spectra recorded in acetone were referenced against residual d_5-acetone (2.05 ppm) while carbon spectra were referenced relative to the d_6-acetone carbonyl singlet (204.1 ppm). Proton spectra recorded in methanol were referenced against residual d_2-methanol (3.40 ppm) while carbon spectra were referenced relative to the central peak of the d_3-methanol heptet (49.3 ppm). Data are recorded as follows: chemical shift (δ), integrated intensity (for proton spectra), multiplicity (**s**: singlet, **d**: doublet, **t**: triplet, **q**: quartet, **m**: multiplet, **dd**, doublet of doublets, etc..., **br** indicates some degree of broadening in the signal), coupling constant(s) (Hz), and assignment (first order analysis of spectra were attempted were possible and, consequently, chemical shifts and coupling constants for multiplets may only be an approximate). Distortionless enhancement by polarisation transfer (DEPT) and the attached proton test (APT) were used in the assignment of carbon spectra.[119] In cases where carbon atoms could not be discrimated the particular peaks in question are either combined, marked with a superscript, or presented as CH_3, CH_2, etc...

Two dimensional NMR experiments were used to assign the molecular framework and were carried out using the following instruments: Varian Gemini 300 and Varian VXR300. The pulse sequences used were homonuclear ($^1H/^1H$) correlation spectroscopy (COSY), double quantum filtered homonulcear ($^1H/^1H$) correlation spectroscopy (DQFCOSY) and heteronuclear ($^1H/^{13}C$) correlation spectroscopy (HETCOR).[119]

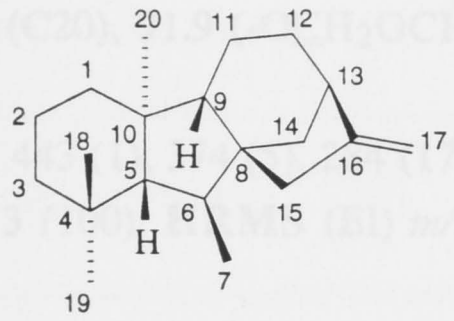
Analytical thin layer chromatography (TLC) was conducted on micro-slides coated with 0.2 mm thick Merck silica gel 60 GF_{254}, or Merck TLC Aluminium sheets silica gel 60 F_{254}. The developed plates were visualised under shortwave ultraviolet light, exposure to iodine vapour and finally stained with 13% (*w/v*) vanillin in concentrated sulfuric acid at 180°C. Flash chromatography was conducted according to the method of Still and coworkers[120] using Merck Kieselgel 60 as the adsorbent and distilled analytical reagent (AR) grade solvents as indicated. Medium pressure liquid chromatgraphy (MPLC) was conducted using a CfG Prominent Duramat® pump, a Water Associate Differential Refractometer R40 diffractometer and Merck Lobar® Fertigsäule Größe LiChroprep® Si60 (40 - 63µm) columns.

Many reagents were commerically available (Aldrich, Merck) and were used as supplied. Where necessary, solvents and reagents used in reactions were purified according to well established procedures.[121] Tetrahydrofuran (THF), diethyl ether (ether) and benzene were purified by distillation from sodium benzophenone ketyl. *N,N*-Dimethylformamide (DMF) was dried by the method of Burfield and Smithers.[122] Dichloromethane, 1,2-dichloroethane and triethylamine were distilled from calcium hydride. Ethanol-free ethereal diazomethane was prepared from Diazald® (N-methyl-N-nitroso-p-toluenesulfonamide) purchased from Aldrich.[123]

Unless otherwise stated, all reactions requiring dry solvent were performed in flame-dried flasks, under a dry nitrogen atmosphere. Reaction temperature refer to the external bath temperature. Reactions requiring sonication were performed by placing the reaction vessel into a Bransonic B221(185W) Ultrasound cleaner bath; the height of the vessel was adjusted so that the solution received maximum agitation. All organic extracts were dried with anhydrous sodium sulfate. After filtration of solutions from drying reagents, the bulk of the solvent was removed on a Büchi rotatory evaporator. The last traces of solvent were removed under high vacuum. Yields are given for isolated product, unless otherwise stated.

NOTES ON NOMENCLATURE

Compounds described in the Experimental have been named as derivatives of *ent*-gibberellane.[5(b)]



ent-gibberellane skeleton

8.2 CHAPTER 2 EXPERIMENTAL

8.2.1 PETERSON OLEFINATION

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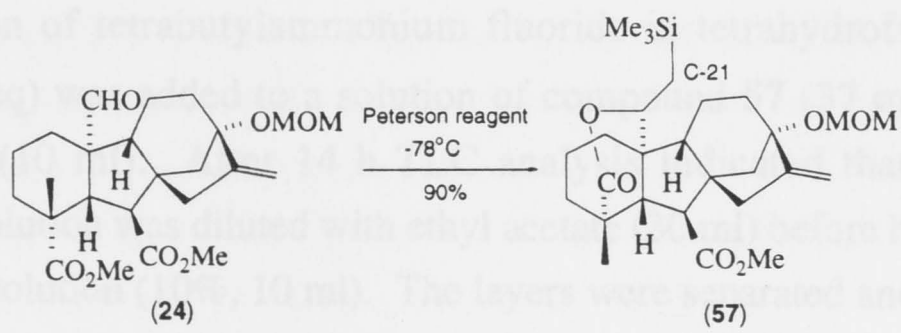
ent-20-Hydroxy-13-methoxymethoxy-20-trimethylsilylmethylgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20 Lactone (57)



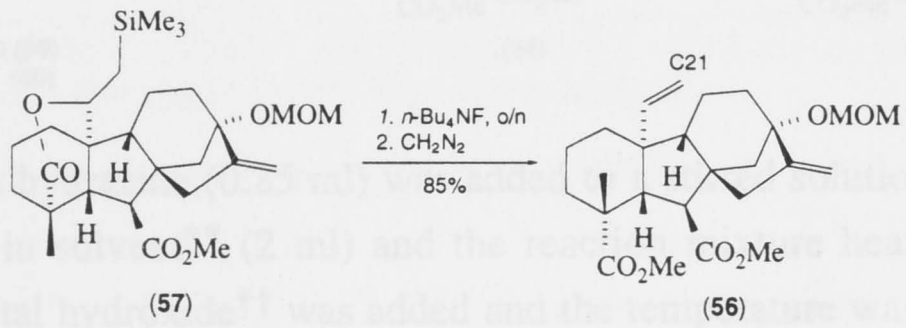
Trimethylsilylmethyl lithium (the Peterson reagent, 300µl, 1M solution, 0.300 mmol, 2.6 eq) was added to a stirred solution of the aldehyde **24** (50mg, 0.115 mmol) in dry tetrahydrofuran (2 ml) under a nitrogen atmosphere at -78°C. The reaction was stirred for 5 min, then water (0.5 ml) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was diluted with ethyl acetate (20 ml) and washed with brine (2x4 ml). The organic phase was dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 3:1) afforded compound **57** (56 mg, 90%) as a colourless oil.
R_f : 0.64 (hexane:ethyl acetate, 2:1). **IR** 1730, 1715 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$) δ 0.13 (9H, s, $-Si(CH_3)_3$), 1.11 (3H, s, H18), 1.00 - 2.40 (17H, m), 2.25 (1H, d, J = 13.2 Hz, H5), 3.15 (1H, d, J = 13.2 Hz, H6), 3.36 (3H, s, $-CH_2OC\underline{H}_3$), 3.69 (3H, s, $-CO_2CH_3$), 4.45 (1H, br d, J = 12.3 Hz, H20),

4.54, 4.73 (2x1H, ABd, J = 7.0 Hz, -OC$\underline{H}_2$OCH$_3$), 5.04 (1H, br s, H17), 5.13 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ -1.0 (-Si(CH_3)$_3$), 17.2 (C11), 21.0 (C2), 22.2 (C18), 27.8 (CH_2), 38.4 (CH_2), 39.5 (CH_2), 41.2 (CH_2), 42.7 (C10), 43.0 (C14), 46.6 (C4), 47.5 (C15), 48.4 (C8), 51.5 (C6), 51.7 (-$CO_2\underline{C}H_3$) 54.9 (C9), 55.4 (-$OCH_2O\underline{C}H_3$), 56.7 (C5), 83.6 (C13), 85.4 (C20), 91.9 (-O$\underline{C}H_2OCH_3$), 108.2 (C17), 152.3 (C16), 173.5 (C19), 175.1 (C7).

MS (EI) *m/z* 490 (M^+, 1%), 443 (1), 374 (5), 284 (17), 149 (22), 129 (11), 111 (10), 97 (23), 95 (15), 83 (29), 73 (100). **HRMS** (EI) *m/z* calcd for M^+, $C_{27}H_{42}O_6Si$: 490.2751; found 490.2751.

Dimethyl *ent*-13-methoxymethoxy-20-methylgibberella-16,20-diene-7,19-dioate (56)



A solution of tetrabutylammonium fluoride in tetrahydrofuran (250 µl, 1M, 0.25 mmol, 3.3 eq) was added to a solution of compound **57** (37 mg, 0.076 mmol) in tetrahydrofuran (10 ml). After 14 h TLC analysis indicated that the reaction was complete. The solution was diluted with ethyl acetate (30 ml) before being acidified with phosphoric acid solution (10%, 10 ml). The layers were separated and the organic phase was washed with water (4x5 ml) to pH = 5. The organic phase was dried over sodium sulfate, filtered and the solvent removed *in vacuo*. The residue was redissolved in diethyl ether (5 ml) and treated with an excess of diazomethane. Purification on silica gel (hexane/ethyl acetate, 7.5:1) afforded the desired olefin **56** (27.6 mg, 85%) as a colourless oil.

R_f : 0.81 (hexane:ethyl acetate, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (3H, s, H18), 0.80 - 2.30 (15H, m), 2.08 (1H, d, *J* = 12.1 Hz, H5), 3.36 (3H, s, -$CH_2OC\underline{H}_3$), 3.59 (1H, d, *J* = 12.1 Hz, H6), 3.62, 3.71 (2x3H, s, -CO_2CH_3), 4.55, 4.75 (2x1H, ABd, *J* = 7.1 Hz, -OC$\underline{H}_2OCH_3$), 5.02 (3H, m, 2xH17 and H21 overlapped), 5.14 (1H, d, *J* = 10.6 Hz, H'21), 5.62 (1H, dd, J_1 = 16.4 Hz, J_2 = 10.6 Hz, H20).

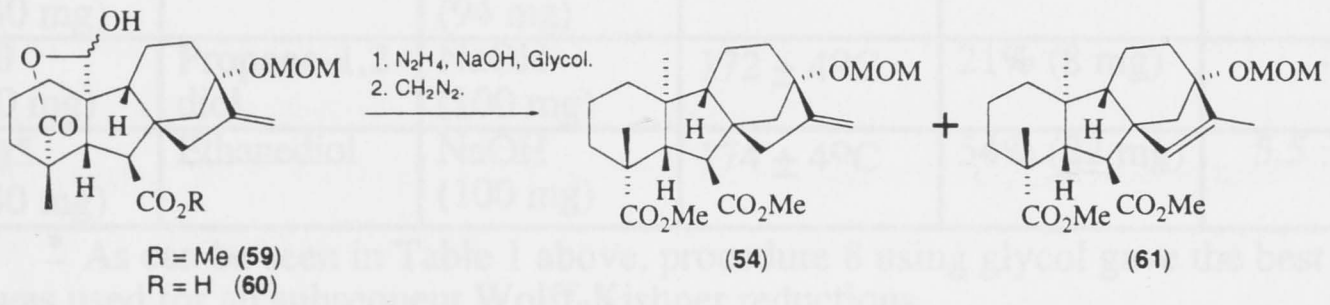
^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5, 19.8 (C2, C11), 27.9 (C18), 34.6 (CH_2), 37.9 (CH_2), 38.0 (CH_2), 44.6, 44.8 (C14, C15), 45.1 (C4), 48.5 (C8), 50.2 (C6), 51.1,

51.4 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$) 51.4 (C10), 55.4 (-$OCH_2O\underline{C}H_3$), 56.7 (C9), 58.3 (C5), 83.7 (C13), 91.8 (-$O\underline{C}H_2OCH_3$), 106.8 (C17), 115.8 (C21), 137.1 (C20), 152.5 (C16), 175.7, 176.7 (C7, C19).

MS (EI) *m/z* 432 (M^+, 1%), 400 (10), 372 (18), 341 (7), 327 (16), 313 (16), 267 (8), 180 (10), 155 (10), 121 (34), 105 (39), 91 (65), 57 (100). **HRMS** (EI) *m/z* calcd for M^+, $C_{25}H_{36}O_6$: 432.2512; found 432.2512.

8.2.2 WOLFF-KISHNER PATHWAY

Wolff-Kishner Reduction: General Procedure



R = Me (**59**)
R = H (**60**)

(**54**) (**61**)

Anhydrous hydrazine (0.25 ml) was added to a stirred solution of the hydroxy lactone **59** or **60** in solvent** (2 ml) and the reaction mixture heated at 100°C for 30 min. Solid metal hydroxide†† was added and the temperature was raised to 116°C for 1 h. Finally, the temperature was raised to 170 - 180°C‡‡ and the reaction left overnight. The mixture was diluted with ethyl acetate/20% 2-butanol (50 ml) and was acidified with phosphoric acid (10%, 10 ml). The layers were separated and the aqueous phase was extracted with the ethyl acetate/2-butanol mixture (2x20 ml). The combined organic phases were washed with brine to pH 4. The organic phase was dried over sodium sulfate, filtered and the solvent removed *in vacuo*. At this point the crude material could be taken and used to make the deprotected material **62**, see next experiment. The residue was dissolved in methanol (10 ml) and treated with an excess of diazomethane, followed by the removal of solvent under a gentle stream of nitrogen. Chromatography on silica gel (hexane/ethyl acetate, 3:1) afforded a mixture of compound **54** and the endocyclic olefin isomer **61** as a colourless oil. The results of these experiments appear in Table 1.

NB: The two compounds **54** and **61** could only be separated by careful MPLC.

Table 1: Wolff-Kishner Redution Results

Starting material (amount)	solvent**	type of base†† (amount)	final heating temp.‡‡	isolated yield % (mg)	nmr ratio exo:endo (54) : (61)
1. **59** (40 mg)	Digol	NaOH (100mg)	175 ± 4°C	27% (11 mg)	-
2. **60** (30 mg)	Digol	NaOH (150mg)	170 ± 4°C	45% (14 mg)	5 : 1
3. **60** (30 mg)	Digol	NaOH (300 mg)	174 ± 4°C	59% (18 mg)	3 : 2
4. **60** (40 mg)	Methyl digol	NaOH (100 mg)	172 ± 4°C	67% (27 mg)	2.5 : 1
5. **60** (40 mg)	Methyl digol	KOH (160 mg)	170 ± 4°C	42% (17 mg)	6 : 1
6. **60** (40 mg)	Methyl digol	LiOH (94 mg)	170 ± 4°C	28% (11 mg)	3 : 1
7. **60** (40 mg)	Propane-1,2-diol	NaOH (100 mg)	172 ± 4°C	21% (8 mg)	-
8. **60*** (40 mg)	Ethanediol	NaOH (100 mg)	174 ± 4°C	54% (22 mg)	5.5 : 1

* As can be seen in Table 1 above, procedure 8 using glycol gave the best results and was used for all subsequent Wolff-Kishner reductions.

Dimethyl *ent*-13-methoxymethoxygibberell-15-ene-7,19-dioate (61)

R_f : 0.77 (hexane:ethyl acetate, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.65 (3H, s, H20), 1.08 (3H, s, H18), 1.67 (3H, s, H17), 0.80 - 2.20 (13H, m), 1.80 (1H, d, J = 12.5 Hz, H5), 3.27 (1H, d, J = 12.5 Hz, H6), 3.38 (3H, s, $-OCH_2OC\underline{H}_3$), 3.67 (6H, s, 7-CO_2CH_3 and 19-CO_2CH_3), 4.59, 4.67 (2x1H, ABd, J = 6.9 Hz, $-OC\underline{H}_2OCH_3$), 5.62 (1H, s, H15).

Dimethyl *ent*-13-methoxymethoxygibberell-16-ene-7,19-dioate (54)

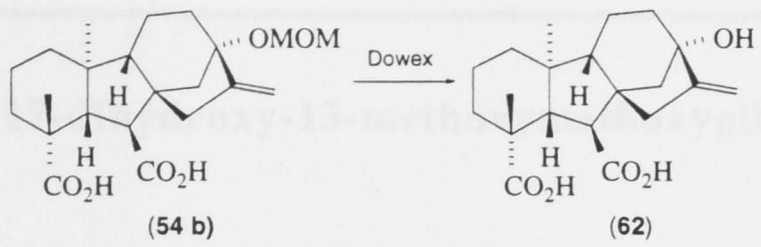
R_f : 0.76 (hexane:ethyl acetate, 2:1). **IR** 1720 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.69 (3H, s, H20), 1.06 (3H, s, H18), 1.00 - 2.30 (15H, m), 1.90 (1H, d, J = 12.1 Hz, H5), 3.38 (4H, m, J = 12.1 Hz, H6 and $-OCH_2OC\underline{H}_3$ overlapped), 3.67, 3.69 (2x3H, s, $-CO_2CH_3$), 4.57, 4.78 (2x1H, ABd, J = 7.1 Hz, $-OC\underline{H}_2OCH_3$), 5.00 (1H, br s, H17), 5.05 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6 (C20), 17.9, 19.5 (C2, C11), 28.3 (C18), 37.6 (C1), 38.5, 39.3 (C3, C12), 43.9, 44.2 (C4, C10), 44.5, 45.2 (C14, C15), 48.2 (C8), 50.7 (C6), 51.3, 51.4 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 55.3 ($-OCH_2O\underline{C}H_3$), 56.1 (C9), 57.8 (C5), 83.7 (C13), 91.8 ($-O\underline{C}H_2OCH_3$), 106.8 (C17), 152.6 (C16), 175.7, 177.4 (C7, C19).

MS (EI) *m/z* 420 (M^+, 3%), 388 (32), 345 (19), 301 (19), 181 (41), 121 (28), 119 (25), 109 (26), 107 (40), 105 (40), 95 (28), 91 (68), 79 (52), 55 (100). **HRMS** (EI) *m/z* calcd. for M^+, $C_{24}H_{36}O_6$: 420.2512; found 420.2510.

ent-13-Hydroxygibberell-16-ene-7,19-dioic Acid (62) (GA_{53})



(54 b) (62)

Dowex resin (80 mg of wet resin) was added to a solution of the crude compound **54(b)** (42 mg, 0.20 mmol) in methanol (6.0 ml) and water (0.80 ml). The reaction was then heated under reflux for 2 h. The solution was diluted with ethyl acetate (20 ml) and filtered through a pad of celite. The solution was then diluted further with ice cold ethyl acetate/20% 2-butanol (20 ml) . This solution was then washed with brine (10 ml), acidified with phosphoric acid solution (10%, 1 ml). The layers were separated and the aqueous phase was extracted with ethyl acetate/20% 2-butanol (2x10 ml). The combined organic phases were washed to pH = 4 with ice cold water. The combined organic phases were dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate/acetic acid, 2:1:0.05) yielded the desired deprotected compound **62** (27 mg, 71%) as a white crystalline solid.

^{1}H NMR (300 MHz, CD_3OD) δ 0.85 (3H, s, H20), 1.14 (3H, s, H18), 0.80 - 2.30 (18H, m), 1.86 (1H, d, *J* = 12.1 Hz, H5), 3.41 (1H, d, *J* = 12.1 Hz, H6), 4.92 (1H, br s, H17), 5.09 (1H, br s, H'17).

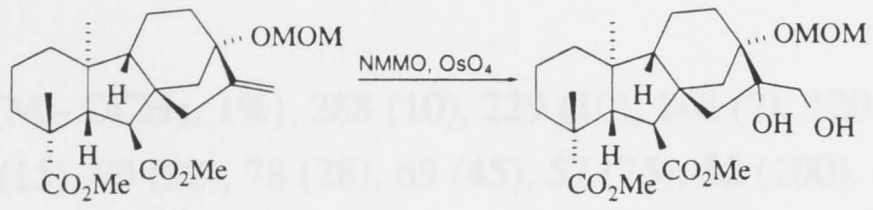
^{13}C NMR (75 MHz, CD_3OD) δ 15.7 (C20), 19.6 (C11), 21.1 (C2), 29.6 (C18), 39.4 (C1), 40.8, 41.1 (C3, C12), 45.6, 45.7 (C4, C10), 46.4 (C14), 49.5 (C8 and C15 overlapped), 52.6 (C6), 58.1 (C9), 59.3 (C5), 79.4 (C13), 106.6 (C17), 157.5 (C16), 179.6 (-CO_2H), 181.3 (-CO_2H).

^{13}C NMR (75 MHz, d_6-acetone) δ 13.2 (C20), 16.8 (C11), 18.3 (C2), 27.1 (C18), 36.6 (C1), 38.2, 38.4 (C3, C12), 42.6 (C4 and C10 overlapped), 43.6 (C14), 46.4, 46.6 (C15, C8), 49.3 (C6), 55.4 (C9), 56.1 (C5), 76.3 (C13), 103.3 (C17), 155.9 (C16), 174.4, 176.6 (C7, C19).

MS (EI) *m/z* 330 (M - H_2O, 21%), 302 (33), 163 (13), 136 (38), 121 (31), 107 (25), 91 (44), 69 (44), 55 (100). **MS** (CI) *m/z* 349 (M+1, 7%), 331 (53), 302 (100), 284 (30), 257 (25), 163 (28), 136 (72), 121 (70), 109 (52). **HRMS** (EI) *m/z* calcd for M - H_2O, $C_{20}H_{26}O_4$: 330.1831; found 330.1832.

8.2.3 C(17)-DIDEUTERIO DERIVATIVES

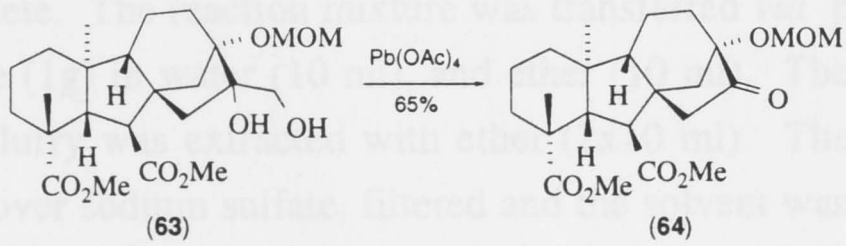
Dimethyl *ent*-16β,17-dihydroxy-13-methoxymethoxygibberellane-7,19-dioate (63)



(54) (63)

To a solution of compound **54** (36mg, 0.086 mmol) in acetone (1 ml) and water (100 µl) was added 4-methylmorpholine-*N*-oxide (12 mg, 0.102 mmol, 1.2eq) followed by a crystal of osmium tetroxide (approximately 2mg). The reaction mixture was left to stir under a nitrogen atmosphere for 14 h after which TLC analysis indicated that the reaction was complete. The reaction mixture was concentrated under reduced pressure, diluted with ethyl acetate (30 ml) and washed with water (10ml), followed by brine (10 ml). The organic phase was dried over sodium sulfate, filtered and the solvent was removed *in vacuo*. Diol **63** was obtained as a brown oil and was used immediately, without further purification.

Dimethyl *ent*-13-methoxymethoxy-16-oxogibberellane-7,19-dioate (64)



(63) (64)

The diol **63** (38 mg crude, 0.085 mmol) was dissolved in dry toluene (2 ml) and lead tetraacetate (120 mg) was added. After 10 min TLC analysis indicated that the reaction was complete. The reaction mixture was diluted with ethyl acetate (30 ml) and was washed with sodium thiosulfate (0.1 M, 2x10 ml) then with brine (10 ml). The combined aqueous phases were extracted with ethyl acetate (2x10 ml). The organic phases were combined, dried over sodium sulfate, filtered and the solvent was removed *in vacuo*. Purification on silica gel (hexane/ethyl acetate, 3:1) yielded the desired ketone **64** (23 mg, 65%) as a white solid.

R_f : 0.50 (hexane:ethyl acetate, 1:1).

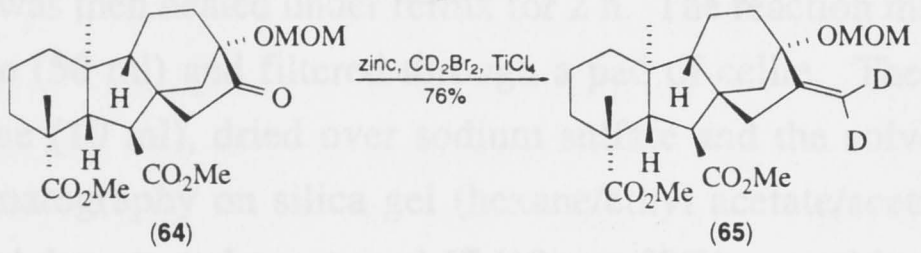
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72 (3H, s, H20), 1.08 (3H, s, H18), 1.20 - 2.30 (15H, m), 1.89 (1H, d, *J* = 12.6 Hz, H5), 3.35 (3H, s, -$OCH_2OC\underline{H}_3$), 3.43 (1H, d,

J = 12.6 Hz, H6), 3.68, 3.71 (2x3H, s, -CO_2CH_3), 4.62, 4.78 (2x1H, ABd, J = 7.4 Hz, -$OC\underline{H}_2OCH_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 15.1 (C20), 17.9 (C11), 19.6 (C2), 28.8 (C18), 32.2 (C1), 37.5 (C3), 39.3, 39.6 (C12, C14), 44.0 (C), 44.3 (C), 44.7 (C), 50.8 (C15), 51.7, 51.8 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 52.3 (C6), 55.9 (C9), 56.9 (C5), 57.1 (-$OCH_2O\underline{C}H_3$), 83.3 (C13), 92.6 (-$O\underline{C}H_2OCH_3$), 174.8, 177.4 (C7, C19), 216.3 (C16).

MS (EI) *m/z* 391 (M - OCH_3, 1%), 288 (10), 229 (10), 148 (7), 120 (7), 118 (7), 107 (10), 104 (17), 93 (15), 90 (32), 78 (28), 69 (45), 57 (75), 55 (100). **HRMS** (EI) *m/z* calcd for M - OCH_3, $C_{22}H_{31}O_6$: 391.2121; found 391.2121.

Dimethyl *ent*-17-dideutero-13-methoxymethoxygibberell-16-ene-7,19-dioate (65)



(64) (65)

The Lombardo reagent[56] approximately 0.7 ml was added *via* a pasteur pipette to a solution of the 16-norketone **64** (33 mg, 0.08 mmol) in dry dichloromethane (1.5 ml) stirring under a nitrogen atmosphere. After 15 min TLC analysis indicated that the reaction was complete. The reaction mixture was transferred *via* pipette to a slurry of sodium bicarbonate (1g) in water (10 ml), and ether (10 ml). The ethereal layer was decanted and the slurry was extracted with ether (2x10 ml). The combined organic phases were dried over sodium sulfate, filtered and the solvent was removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 3:1) afforded the desired dideutero compound **65** (25 mg, 76%) as a colourless oil.

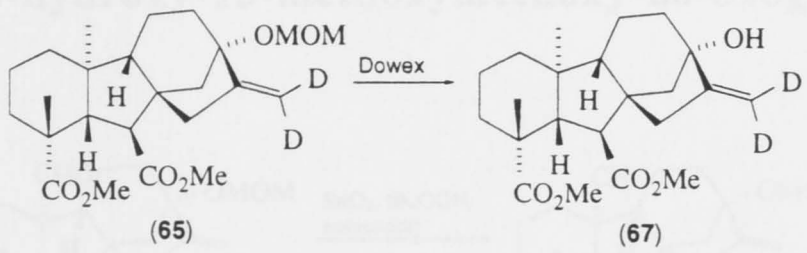
R_f : 0.85 (hexane:ethyl acetate, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.69 (3H, s, H20), 1.06 (3H, s, H18), 1.00 - 2.30 (15H, m), 1.89 (1H, d, J = 12.1 Hz, H5), 3.37 (3H, s, -$OCH_2OC\underline{H}_3$), 3.38 (1H, d, J = 12.1 Hz, H6), 3.67, 3.69 (2x3H, s, -CO_2CH_3), 4.57, 4.77 (2x1H, ABd, J = 7.1 Hz, -$OC\underline{H}_2OCH_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6 (C20), 17.9 (C11), 19.5 (C2), 28.3 (C18), 37.6 (C1), 38.5, 39.3 (C3, C12), 43.9, 44.1 (C4, C10), 44.4, 45.2 (C14, C15), 48.2 (C8), 50.6 (C6), 51.3, 51.4 (7-$CO_2\underline{C}H_3$ and 19-$CO_2\underline{C}H_3$), 55.3 (-$OCH_2O\underline{C}H_3$), 56.1 (C9), 57.7 (C5), 83.7 (C13), 91.7 (-$O\underline{C}H_2OCH_3$), 152.6 (C16), 175.7, 177.4 (C7, C19).

MS (EI) *m/z* 390 (M^+, 1%), 180 (4), 148 (12), 107 (10), 97 (10), 92 (15), 90 (20), 83 (17), 80 (23), 71 (33), 68 (57), 58 (45), 57 (100). **HRMS** (EI) *m/z* calcd for M - CH_3OH, $C_{23}H_{30}O_5D_2$: 390.2375; found 390.2374.

Dimethyl *ent*-17-dideutero-13-hydroxygibberell-16-ene-7,19-dioate (67)



(65) (67)

Dowex 50W-X2 resin (40 mg of wet resin) was added to a solution of the compound **65** (26 mg, 0.062 mmol) in methanol (3.0 ml) and water (0.40 ml). The reaction mixture was then heated under reflux for 2 h. The reaction mixture was diluted with ethyl acetate (50 ml) and filtered through a pad of celite. The filtrate was then washed with brine (10 ml), dried over sodium sulfate and the solvent was removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate/acetic acid, 2:1:0.05) yielded the desired deprotected compound **67** (12 mg, 52%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.65 (3H, s, H20), 1.01 (3H, s, H18), 0.80 - 2.20 (16H, m), 1.86 (1H, d, *J* = 12.2 Hz, H5), 3.30 (1H, d, *J* = 12.2 Hz, H6), 3.61, 3.64 (2x3H, s, $-CO_2CH_3$).

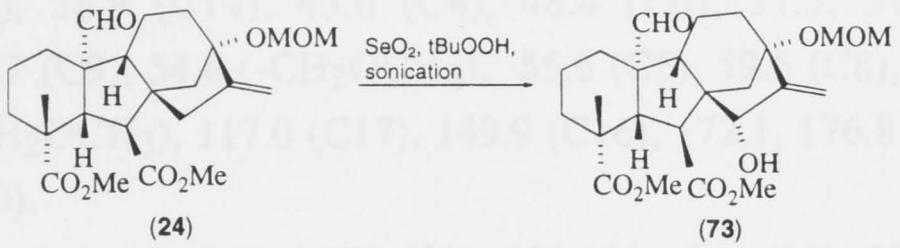
^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6 (C20), 18.3 (C11), 19.8 (C2), 28.5 (C18), 37.8 (C1), 39.3, 39.6 (C3, C12), 44.0, 44.4 (C4, C10), 44.7 (C14), 48.0 (C15), 48.2 (C8), 51.0 (C6), 51.3, 51.4 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 56.5 (C9), 57.7 (C5), 78.6 (C13), 157.0 (C16), 175.6, 177.4 (C7, C19).

MS (EI) *m/z* 346 (M - CH_3OH, 12%), 318 (97), 303 (14), 286 (15), 259 (27), 243 (15), 161 (16), 121 (24), 107 (37), 93 (36), 81 (52), 69 (58), 55 (100). **HRMS** (EI) *m/z* calcd for M - CH_3OH, $C_{21}H_{26}O_4D_2$: 420.2512; found 420.2510.

8.3 CHAPTER 3 EXPERIMENTAL

8.3 15β-HYDROXY-C(20)-GIBBERELLINS

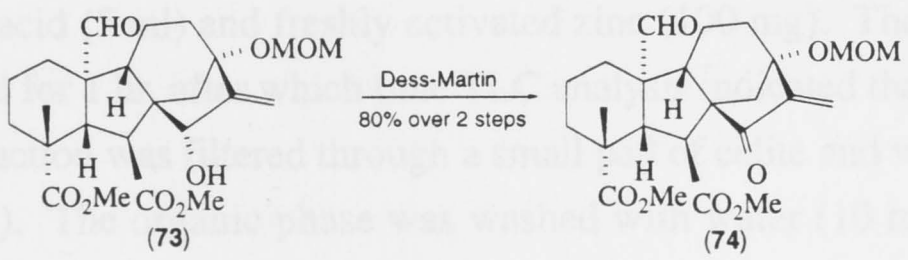
Dimethyl *ent*-15β-hydroxy-13-methoxymethoxy-20-oxogibberell-16-ene-7,19-dioate (73)



Selenium dioxide (50 mg, 0.450 mmol, 3.3eq.), followed by one drop of *t*-butylhydroperoxide solution were added to a solution of the compound **24** (59 mg, 0.145 mmol) dissolved in dry dichloromethane (5 ml). The mixture was sonicated for 3 h, then the solution was diluted with ethyl acetate (30 ml) and washed with dilute hydrochloric acid (10 ml) and water (10 ml). The combined aqueous phases were extracted with ethyl acetate (2x10 ml). The combined organic phases were washed with sodium bicarbonate (10 ml), dried over sodium sulfate, filtered, and the solvent was removed *in vacuo*. The yellow residue **73** was used immediately in the next step.

R_f : 0.42 (ethyl acetate/hexane, 1:1)

Dimethyl *ent*-13-methoxymethoxy-15,20-dioxogibberell-16-ene-7,19-dioate (74)



The 15α-hydroxy compound **73** (60 mg, 0.136 mmol) was dissolved in dry dichloromethane (15 ml) and Dess-Martin reagent (116 mg, 0.273 mmol, approximately 2 eq.) was added. After 10 min the reaction appeared as a cloudy white solution. The reaction mixture was diluted with dichloromethane (20 ml) and saturated sodium bicarbonate solution containing 7% sodium thiosulfate (20 ml). The solution was left stirring for 20 min, the layers were separated and the organic phase was washed with saturated sodium bicarbonate solution (2x10 ml), then with brine (15 ml), dried over sodium sulfate, filtered and the solvent was removed *in vacuo*. Purification by silica gel

chromatography (hexane/ethyl acetate, 3:1) yielded the desired enone **74** (49 mg, 80% from the starting material **24**) as a white foam.

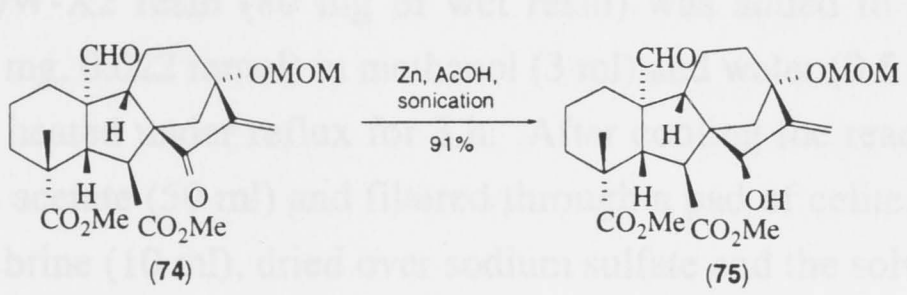
R_f : 0.74 (ethyl acetate:hexane, 1:1). **IR** 1750, 1725, 1715 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (3H, s, H18), 1.20 - 2.50 (13H, m), 2.43 (1H, d, J = 12.3 Hz, H5), 3.41 (3H, s, -$OCH_2OC\underline{H}_3$), 3.63 (2x3H, s, -CO_2CH_3), 3.93 (1H, d, J =12.8 Hz, H6), 4.68, 4.80 (2x1H, ABd, J = 7.3 Hz, -$OC\underline{H}_2OCH3$), 5.45 (1H, s, H17), 6.08 (1H, s, H'17), 9.71 (1H, s, H20).

^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0 (C11), 20.4 (C2), 29.0 (C18), 32.5 (C3), 35.9 (C1), 37.7 (C12), 38.9 (C14), 45.6 (C4), 48.4 (C6), 51.5, 51.6 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 52.7 (C9), 54.8 (-$CH_2O\underline{C}H_3$), 55.6 (C5), 59.6 (C8), 61.1 (C10), 80.3 (C13), 91.5 (-$O\underline{C}H_2OCH_3$), 117.0 (C17), 149.9 (C16), 172.1, 176.8 (C7, C19), 203.5 (C15), 205.1 (C20).

MS (EI) *m/z* 420 (M^+-CO, 24%), 388 (52), 360 (56), 344 (38), 326 (46), 315 (60), 299 (94), 285 (52), 255 (100), 239 (62), 227 (54), 145 (50), 111 (70). 91 (66), 55 (100). **HRMS** (EI) *m/z* calcd for M^+-CO, $C_{23}H_{32}O_7$: 420.2148; found 420.2150.

Dimethyl *ent*-15α-hydroxy-13-methoxymethoxy-20-oxogibberell-16-ene-7,19-dioate (75)



(74) (75)

To a solution of the enone **74** (49 mg, 0.109 mmol) dissolved in benzene (10 ml) was added acetic acid (5 ml) and freshly activated zinc (100 mg). The reaction mixture was then sonicated for 1 hr. after which time TLC analysis indicated that the reaction was complete. The reaction was filtered through a small pad of celite and washed thoroughly with ether (30 ml). The organic phase was washed with water (10 ml), with saturated sodium bicarbonate solution (10 ml), and brine (10 ml). The organic phase was dried over sodium sulfate, filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (hexane/ethyl acetate, 2:1) yielded the desired 15β-hydroxy compound **75** (45 mg, 91%) containing a small amount of an impurity (approximately 10%, most likely the 1,4 reduction product) that could not be removed by flash chromatograhy.

R_f : 0.66 (ethyl acetate:hexane, 1:1). **IR** 1715 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (3H, s, H18), 0.80 - 2.50 (14H, m), 2.10 (1H, d, J = 12.8 Hz, H5), 3.35 (3H, s, -$OCH_2OC\underline{H}_3$), 3.63, 3.79 (2x3H, s, -CO_2CH_3), 3.92

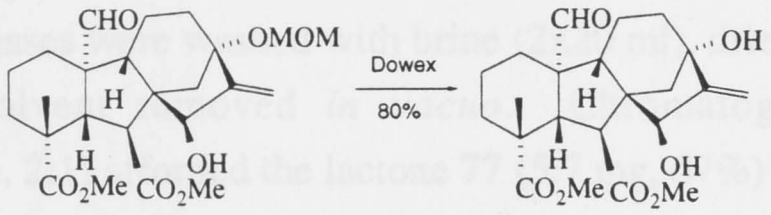
(1H, d, J = 12.8 Hz, H6), 4.07 (1H, m, H15), 4.53, 4.76 (2x1H, ABd, J = 7.3 Hz, -OC$\underline{H}_2$OCH$_3$), 5.23 (1H, s, H17), 5.31 (1H, s, H'17), 9.65 (1H, s, H20).

^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8 (C11), 20.7 (C2), 27.6 (C18), 32.4 (C3), 37.6 (C1), 38.6 (C12), 38.8 (C14), (C4 not observed), 45.1 (C6), 50.1 (C9), 51.7, 52.7 (7-CO$_2\underline{C}$H$_3$, 19-CO$_2\underline{C}$H$_3$), 52.6 (C8), 55.4 (-OCH$_2$O$\underline{C}$H$_3$), 58.4 (C5), 59.3 (C10), 76.9 (C15), 81.5 (C13), 91.9 (-O$\underline{C}$H$_2$OCH$_3$), 109.9 (C17), 153.7 (C16), 176.2, 178.0 (C7, C19), 205.7 (C20).

MS (EI) *m/z* 418 (M$^+$-CH$_3$OH, 16%), 373 (15), 356 (26), 328 (28), 300 (30), 285 (34), 267 (28), 239 (26), 227 (100), 195 (30), 165 (32), 145 (28). 91 (32), 55 (30).

HRMS (EI) *m/z* calcd. for M$^+$- CH$_3$OH, $C_{23}H_{30}O_7$: 418.1992; found 418.1990.

Dimethyl *ent*-15α,13-dihydroxy-20-oxogibberell-16-ene-7,19-dioate (76)



(75) (76)

Dowex 50W-X2 resin (80 mg of wet resin) was added to a solution of the compound **75** (10 mg, 0.022 mmol) in methanol (3 ml) and water (0.5 ml). The reaction mixture was then heated under reflux for 3 h. After cooling the reaction mixture was diluted with ethyl acetate (50 ml) and filtered through a pad of celite. The filtrate was then washed with brine (10 ml), dried over sodium sulfate and the solvent was removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 1:1) afforded the desired dihydroxy aldehyde **76** (7.2 mg 80%) as a solid, plus some starting material **75** (1.2 mg, 13%).

R$_f$: 0.37 (ethyl acetate:hexane, 1:1). **IR** 1710 cm^{-1}.

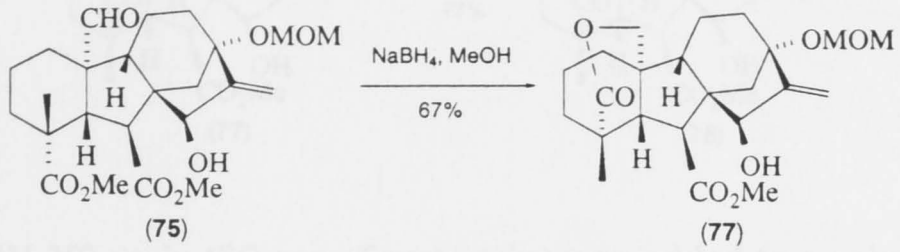
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (3H, s, H18), 1.00 - 2.50 (15H, m), 2.12 (1H, d, J = 13.0 Hz, H5), 3.63, 3.79 (2x3H, s, -CO$_2$CH$_3$), 3.94 (1H, d, J = 13.0 Hz, H6), 4.14 (1H, m, H15), 5.26 (1H, d, J = 2.5 Hz, H17), 5.34 (1H, d, J = 3.0 Hz, H'17), 9.64 (1H, s, H20).

^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1 (C11), 20.7 (C2), 27.8 (C18), 32.4 (C1), 37.5 (C3), 39.2 (C12), 42.2 (C14), 44.8 (C6), 45.2 (C4), 50.0 (C9), 51.7, 52.6 (7-CO$_2\underline{C}$H$_3$, 19-CO$_2\underline{C}$H$_3$), 53.2 (C8), 58.2 (C5), 59.3 (C10), 76.3 (C13), 76.4 (C15), 109.0 (C17), 157.5 (C16), 176.3, 177.8 (C7, C19), 205.6 (C20).

MS (EI) *m/z* 374 (M$^+$-CH$_3$OH, 17%), 346 (28), 328 (66), 300 (100), 286 (36), 268 (48), 241 (70), 183 (67), 159 (38), 145 (43), 129 (36), 105 (41), 91 (51), 55 (35).

HRMS (EI) *m/z* calcd. for M$^+$- CH3OH, $C_{21}H_{26}O_6$: 374.1729; found 374.1729.

ent-15α,20-Dihydroxy-13-methoxymethoxygibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (77)



Sodium borohydride (4 mg, 0.10 mmol) was added to a solution of the aldehyde **75** (9 mg, 0.02 mmol) in methanol (5 ml) at 0°C. After 1 h TLC analysis showed that the reaction was complete. The solution was diluted with ethyl actetate (50 ml) and acidified with sodium dihydrogen phosphate solution (20%, 20 ml). The layers were separated and the aqueous phase was extracted with ethyl acetate (2x10 ml). The combined organic phases were washed with brine (2x20 ml), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 2:1) afforded the lactone **77** (5.7 mg, 67%) as a colourless oil.

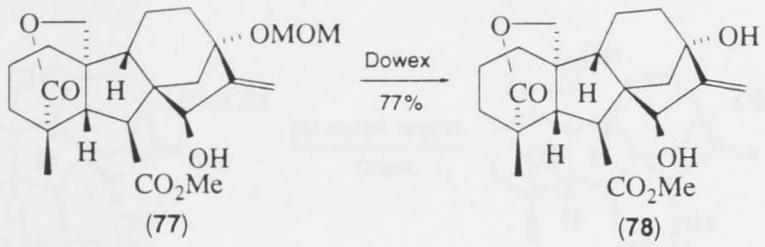
R_f : 0.28 (hexane:ethyl acetate, 2:1). **IR** 1723 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (3H, s, H18), 1.00 - 2.30 (14H, m), 2.11 (1H, d, J = 12.8 Hz, H5), 2.81 (1H, d, J = 12.8 Hz, H6), 3.36 (3H, s, $-OCH_2O\underline{C}H_3$), 3.76 (3H, s, $-CO_2CH_3$), 3.97 (1H, m, H15), 4.15 (1H, d, J_{gem} = 11.2 Hz, 20-pro-S-H), 4.37 (1H, dd, J_{gem} = 11.2 Hz, $J_{20R,1\beta}$ = 2.6 Hz, 20-pro-R-H), 4.53, 4.74 (2x1H, ABd, J = 7.3 Hz, $-OC\underline{H}_2OCH_3$), 5.26 (1H, d, J = 3 Hz, H17), 5.30 (1H, d, J = 2.7 Hz, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 15.6 (C11), 20.6 (C2), 22.8 (C18), 37.3, 37.6 (C3, C1), 38.7 (C12), 39.8 (C14), 41.1 (C10), 42.6 (C4), 44.1 (C6), 51.8 ($-CO_2\underline{C}H_3$), 52.4 (C8), 52.8 (C5), 55.3 (C9), 55.5 ($-OCH_2O\underline{C}H_3$), 75.1 (C20), 77.2 (C15), 81.9 (C13), 92.0 ($-O\underline{C}H_2OCH_3$), 110.0 (C17), 154.3 (C16), 174.9, 176.5 (C7, C19).

MS (EI) *m/z* 420 (M^+, 8%), 391 (13), 375 (17), 359 (23), 343 (62), 328 (18), 298 (20), 269 (29), 227 (100), 195 (31), 145 (23), 105 (21), 91 (26), 55 (29). **HRMS** (EI) *m/z* calcd for M^+, $C_{23}H_{32}O_7$: 420.2148; found 420.2150.

ent-13β,15α,20-Trihydroxygibberell-16-ene-7,19-dioic Acid 7-Methyl ester 19,20-Lactone (78)



Dowex 50W-X2 resin (80 mg of wet resin) was added to a solution of the lactone **77** (5.5 mg, 0.013 mmol) in methanol (3.3 ml) and water (0.66 ml). The reaction mixture was then refluxed for 3 hrs., after which time TLC analysis indicated that the reaction was complete. The reaction mixture was diluted with ethyl acetate (50 ml) and filtered through a pad of celite. The filtrate was then washed with brine (10 ml), dried over sodium sulfate and the solvent was removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 2:1 - 1:2) afforded the desired dihydroxy lactone **78** (3.8 mg, 77%) as a slightly off white solid.

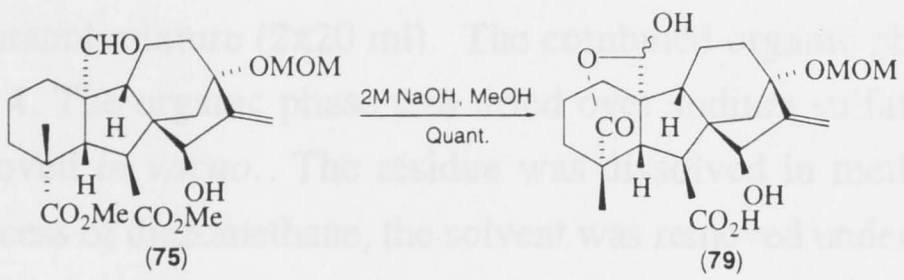
R_f : 0.16 (hexane:ethyl acetate, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (3H, s, H18), 1.20 - 2.30 (15H, m), 2.13 (1H, d, J = 12.7 Hz, H5), 2.82 (1H, d, J = 12.7 Hz, H6), 3.76 (3H, s, -$CO_2C\underline{H}_3$), 4.05 (1H, br s, H15), 4.15 (1H, d, J_{gem} = 13.2 Hz, 20-pro-S-H), 4.37 (1H, dd, J_{gem} = 13.2 Hz, $J_{20,1\beta}$ = 2.2 Hz, 20-pro-R-H), 5.24 (1H, d, J = 2.6 Hz, H17), 5.37 (1H, d, J = 3.0 Hz, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9 (C11), 20.6 (C2), 22.9 (C18), 37.6 (C1), 39.1, 39.8 (C3, C12), 41.1 (C10), 41.2 (C14), 42.6 (C4), 43.8 (C6), 52.7 (C5), 53.0 (-CO_2CH_3), 53.0 (C8), 55.0 (C9), 75.1 (C20), 76.6 (C15), 76.7 (C13), 109.1 (C17), 158.2 (C16), 174.9, 176.3 (C7, C19).

MS (EI) *m/z* 376 (M^+, 20%), 344 (83), 316 (23), 298 (49), 260 (35), 241 (32), 183 (100), 159 (55), 145 (42), 105 (42), 91 (51), 79 (32), 55 (43). **HRMS** (EI) *m/z* calcd for M^+, $C_{21}H_{28}O_6$: 376.1886; found 376.1887.

ent-15α,20,20-Trihydroxy-13-methoxymethoxygibberell-16-ene-7,19-dioic Acid 19,20-Lactone (79)

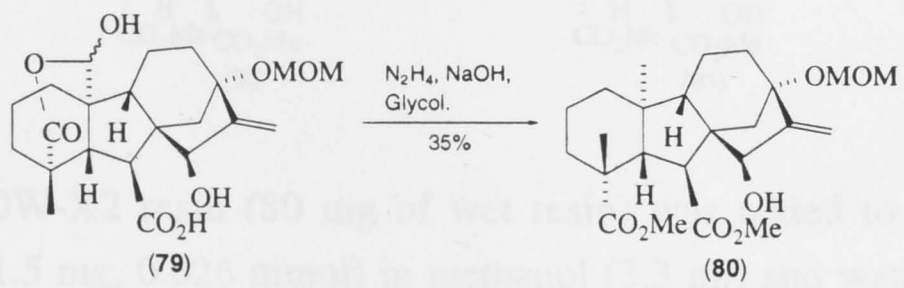


The aldehyde **75** (25 mg, 0.055 mmol) was dissolved in methanol (0.5 ml) and 2M sodium hydroxide solution (3 ml). The reaction mixture was heated at reflux for 6 h. After cooling the mixture was diluted with ethyl acetate/20% 2-butanol (50 ml) and was acidified with phosphoric acid (10%, 10 ml). The layers were separated and the aqueous phase was extracted with the ethyl acetate/2-butanol mixture (2x20 ml). The combined organic phases were washed with brine to pH 4. The organic phase was dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification on silica gel (hexane/ethyl acetate/ acetic acid, 2:1:0.1) provided the hydroxy lactone **79** (23 mg, 100%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (3H, s, H18), 1.20 - 2.50 (19H, m), 2.15 (1H, d, J = 13.4 Hz, H5), 3.38 (4H, s, $-OCH_2OC\underline{H}_3$ and H6 overlapped), 4.20 (1H, br s, H15), 4.55, 4.79 (2x1H, ABd, J = 7.3 Hz, $-OC\underline{H}_2OCH_3$), 5.25 (1H, br s, H17), 5.29 (1H, br s, H'17), 5.80 (1H, br s, H20).

MS (EI) *m/z* 404 (M^+-H_2O, 25%), 376 (12), 359 (28), 331 (28), 314 (38), 285 (50), 257 (59), 239 (61), 213 (62), 149 (43), 91 (58), 71 (65), 57 (100). **HRMS** (EI) *m/z* calcd. for M^+-H_2O, $C_{22}H_{28}O_7$: 404.1835; found 404.1834.

Dimethyl _ent_-15α-hydroxy-13-methoxymethoxygibberell-16-ene-7,19-dioate (80)



Anhydrous hydrazine (0.25 ml) was added to a solution of the hydroxy lactone **79** (23 mg, 0.055 mmol) in ethylene glycol (2 ml) and the reaction mixture was heated at 100°C for 30 min. Half a pellet of sodium hydroxide (approximately 200 mg) was added and the temperature was raised to 116°C for 1 h. Finally the temperature was

raised to 180°C and the reaction left overnight. After cooling the mixture was diluted with ethyl acetate/20% 2-butanol (50 ml) and was acidified with phosphoric acid (10%, 10 ml). The layers were separated and the aqueous phase was extracted with the ethyl acetate/2-butanol mixture (2x20 ml). The combined organic phases were washed with brine to pH 4. The organic phase was dried over sodium sulfate, filtered and the solvent was removed *in vacuo*. The residue was dissolved in methanol (10 ml) and treated with an excess of diazomethane, the solvent was removed under a gentle stream of nitrogen and finally purification on silica gel (hexane/ethyl acetate, 3:1) afforded compound **80** (8.5 mg, 35%) as a a colourless oil.

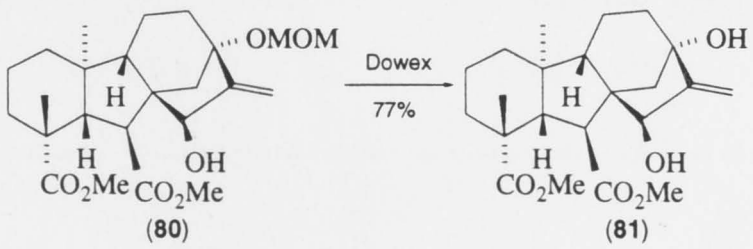
R_f : 0.65 (hexane:ethyl acetate, 2:1). **IR** 1720 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.69 (3H, s, H20), 1.04 (3H, s, H18), 1.00 - 2.20 (14H, m), 1.78 (1H, d, J = 12.5 Hz, H5), 3.36 (3H, s, $-OCH_2O\underline{C}H_3$), 3.39 (1H, d, J = 12.5 Hz, H6), 3.67, 3.75 (2x3H, s, $-CO_2CH_3$), 4.02 (1H, m, H15), 4.56, 4.77 (2x1H, ABd, J = 7.3 Hz, $-OC\underline{H}_2OCH_3$), 5.21 (1H, d, J = 3.1 Hz, H17), 5.31 (1H, d, J = 2.5 Hz, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 15.1 (C20), 17.3 (C11), 19.5 (C2), 28.3 (C18), 37.5 (C1), 38.6, 39.0 (C3, C12), 40.5 (C14), 43.4, 44.3 (C4, C8), 45.2 (C6), 50.8 (C9), 51.4, 52.3 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 52.9 (C10), 55.4 ($-OCH_2O\underline{C}H_3$), 59.5 (C5), 77.1 (C15), 81.8 (C13), 91.8 ($-O\underline{C}H_2OCH_3$), 108.9 (C17), 153.7 (C16), 177.2, 178.8 (C7, C19).

MS (EI) *m/z* 436 (M^+, 8%), 404 (49), 376 (34), 359 (100), 342 (52), 299 (52), 271 (45), 255 (38), 227 (33), 197 (31), 149 (39), 91 (37). **HRMS** (EI) *m/z* calcd for M^+, $C_{24}H_{36}O_7$: 436.2461; found 436.2463.

Dimethyl *ent*-13,15α-Dihydroxygibberell-16-ene-7,19-dioate (81)



(80) (81)

Dowex 50W-X2 resin (80 mg of wet resin) was added to a solution of the compound **80** (11.5 mg, 0.026 mmol) in methanol (3.3 ml) and water (0.66 ml). The reaction mixture was then heated under reflux for 4 h. The solution was diluted with ethyl acetate (50 ml) and filtered through a pad of celite. The filtrate was then washed with brine (10 ml), dried over sodium sulfate and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 1:1) afforded compound **81** (7.3 mg 77%) as a white solid.

R_f : 0.45 (hexane:ethyl acetate, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.68 (3H, s, H20), 1.05 (3H, s, H18), 0.80 - 2.30 (15H, m), 1.81 (1H, d, J = 12.6 Hz, H5), 3.39 (1H, d, J = 12.6 Hz, H6), 3.67, 3.76 (2x3H, s, $-CO_2CH_3$), 4.08 (1H, m, H15), 5.25 (1H, d, J = 2.6 Hz, H17), 5.30 (1H, d, J = 3.0 Hz, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 15.2 (C20), 17.6 (C11), 19.5 (C2), 28.5 (C18), 37.5 (C1), 39.1, 39.3 (C3, C12), 43.4 (C4) 43.9 (C14), 44.4 (C8), 44.9 (C6), 50.8, 52.3 ($7\text{-}CO_2\underline{C}H_3$, $19\text{-}CO_2\underline{C}H_3$), 51.5 (C9), 53.3 (C10), 59.3 (C5), 76.7 (C15), 108.3 (C17), 157.6 (C16), 177.3, 178.7 (C7, C19); C13 obscured by solvent

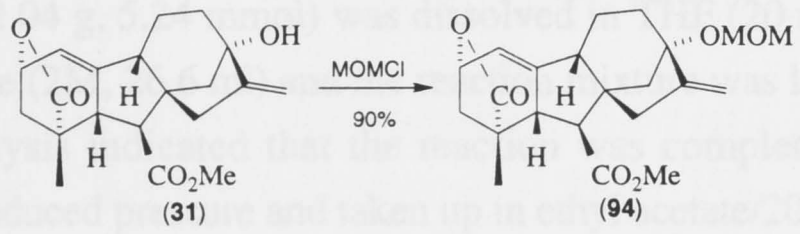
^{13}C NMR (75 MHz, d_6-acetone) δ 14.9 (C20), 17.8 (C11), 19.7 (C2), 28.2 (C18), 37.8 (C1), 39.4, 40.2 (C3, C12), 43.4 (C4), 44.0 (C14), 44.4 (C8), 45.2 (C6), 50.9, 51.7 ($7\text{-}CO_2\underline{C}H_3$, $19\text{-}CO_2\underline{C}H_3$), 51.0 (C9), 53.3 (C10), 58.7 (C5), 75.7 (C13), 76.6 (C15), 106.7 (C17), 159.5 (C16), 176.9, 177.8 ($7\text{-}\underline{C}O_2CH_3$, $19\text{-}\underline{C}O_2CH_3$).

MS (EI) *m/z* 392 (M^+, 2%), 374 (3), 360 (100), 342 (20), 332 (66), 314 (39), 300 (30), 285 (18), 272 (31), 255 (39), 173 (30), 159 (30), 105 (30), 91 (30), 69 (22), 55 (26). **HRMS** (EI) *m/z* calcd for $M^+ - CH_3OH$, $C_{21}H_{28}O_5$: 360.1937; found 360.1936.

8.4 Chapter 4 Experimental

8.4.1 2β,13α-Dihydroxy Series

ent-2β-Hydroxy-13-methoxymethoxy-20-norgibberella-1(10),16-diene-7,19-dioic Acid 7-Methyl Ester 19,2-Lactone (94)



(31) (94)

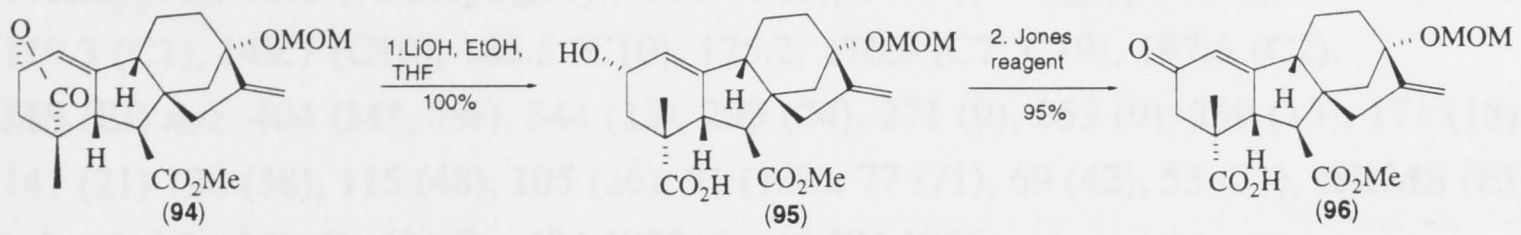
DIPEA (25.0 ml, 144 mmol, 10eq), chloromethyl methyl ether (11.0 ml, 144 mmol, 10eq) plus a catalytic amount of DMAP was added to a solution of compound **31**[#] (4.97 g, 14.4 mmol) in dry dichloromethane (100 ml) at 0°C under an atmosphere of nitrogen. The reaction mixture was left in the cold bath to warm up to room temp. overnight. TLC analysis indicated that the reaction was complete, so sat. sodium bicarbonate solution (20 ml) was added and the reaction mixture left stirring for 20 min. The layers were separated and the aqueous phase was back-extracted with dichloromethane (2x20 ml). The combined organic phases were washed with hydrochloric acid (1M, 2x20 ml), brine (2x20ml), dried over sodium sulfate, filtered and the solvent was removed *in vacuo.* Chromatograhy on silica gel (hexane/ethyl acetate, 2:1) afforded compound **94** (5.03 g, 90%) as a colourless oil.

R_f : 0.75 (hexane:ethyl acetate, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 , (3H, s, H18), 1.50 - 2.60 (11H, m), 2.59 (1H, d, J = 6.2 Hz, H6), 3.19 (1H, m, H5), 3.35 (3H, s, -$OCH_2OC\underline{H}_3$), 3.73 (3H, s, -CO_2CH3), 4.58, 4.76 (2x1H, ABd, J = 7.0 Hz, -$OC\underline{H}_2OCH_3$), 4.85 (1H, t, J = 5.3 Hz, H2), 5.05 (2H, br s, H17), 5.94 (1H, br s, H1).

[#] This material was synthesised by the procedure shown in Scheme 5, p 10.

ent-13-Methoxymethoxy-2-oxo-20-norgibberella-1(10),16-diene-7,19-dioic Acid 7-Methyl ester (96)



Lactone **94** (2.04 g, 5.24 mmol) was dissolved in THF (20 ml), ethanol (41 ml), and lithium hydroxide (2M, 26.6 ml) and the reaction mixture was left stirring under N_2. After 4 h, TLC analysis indicated that the reaction was complete. The sample was concentrated under reduced pressure and taken up in ethyl acetate/20% 2-butanol (80 ml). The aqueous phase was carefully acidified to (pH 5) with sodium dihydrogen phosphate solution (20%), the layers separated, and the aqueous phase extracted with the ethyl acetate/2-butanol mixture (2x30 ml). The combined organic phases were dried over sodium sulfate, filtered and the solvent was removed *in vacuo* to yield a white foam **95** (2.13 g, 100%). This material was used immediately without further purification.
R_f : 0.23 (hexane:ethyl acetate:acetic acid, 1:1:0.1). **IR** 3400, 1720, 1700 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 , (3H, s, H18), 0.80 - 2.70 (13H, m), 2.80 (1H, br s, H5), 3.12 (1H, d, J = 4.3 Hz, H6), 3.35 (3H, s, -$OCH_2OC\underline{H}_3$), 3.71 (3H, s, -CO_2CH_3), 4.27 (1H, br s, H2), 4.57, 4.77 (2x1H, ABd, J = 7.0 Hz, -$OC\underline{H}_2OCH_3$), 5.03 (2H, br s, H17), 5.53 (1H, br s, H1).

Compound **95** (2.13 g, 5.24 mmol) was dissolved in acetone (30 ml) and cooled to 0°C, Jones' reagent [65] was then added dropwise to the vigorously stirred solution until a slight excess was present. After 5 min the excess of Jones' reagent was destroyed with 2-propanol. The solution was concentrated under reduced pressure, then the thick green residue was diluted with ethyl acetate containing/20% 2-butanol (80 ml) and washed with sodium dihydrogen phosphate solution (20%, 2x20 ml). The aqueous layer was back-extracted with the ethyl acetate/2-butanol mixture (2x20 ml). The combined organic phases were dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate/acetic acid, 2:1:0.1) produced the α,β-unsaturated keto acid **96** (2.02 g, 95% over two steps) as a slightly off white solid, which crystallised from ethyl acetate/hexane.
R_f : 0.58 (hexane:ethyl acetate, 1:1). **IR** 3400, 1720, 1665 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 , (3H, s, H18), 1.30 - 2.90 (9H, m), 3.21 (1H, d, J = 4.3 Hz, H6), 3.32 (3H, s, -$OCH_2OC\underline{H}_3$), 3.37 (1H, m, H5), 3.75 (3H, s, -CO_2CH_3), 4.56, 4.73 (2x1H, ABd, J = 7.1 Hz, -$OC\underline{H}_2OCH_3$), 5.05 (2H, br s, H17), 5.90 (1H, br s, H1).

^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1 (C11), 24.9 (C18), 36.3 (C12), 38.7 (C15), 44.5 (14), 47.2 (C9), 47.8 (C8), 48.4 (C3), 48.9 (C6), 50.0 (C4), 52.0 (C5 and $-CO_2\underline{C}H_3$ overlapped), 55.1 ($-OCH_2O\underline{C}H_3$), 83.9 (C13), 91.3 (13-$O\underline{C}H_2OCH_3$), 107.5 (C17), 119.3 (C1), 149.7 (C16), 166.5 (C10), 175.2, 176.9 (C7, C19), 197.6 (C2).
MS (EI) *m/z* 404 (M^+, 7%), 344 (13), 299 (24), 271 (9), 255 (9), 239 (15), 171 (18), 141 (21) 128 (38), 115 (48), 105 (26), 91 (100), 77 (71), 69 (42), 55 (71). **HRMS** (EI) *m/z* calcd for M^+, $C_{22}H_{28}O_7$: 404.1835; found 404.1835.

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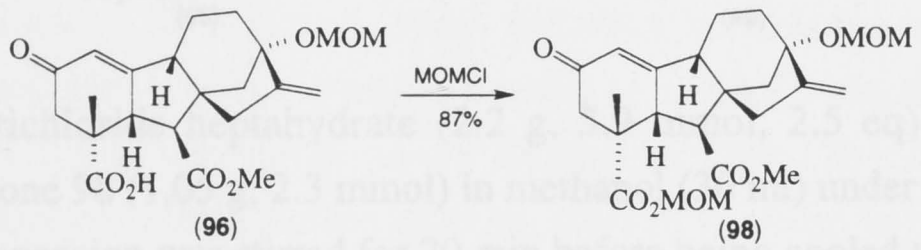
ent-13-Methoxymethoxy-2-oxo-20-norgibberella-1(10),16-diene-7,19-dioic Acid 7-Methyl Ester 19-Methoxymethyl Ester (98)



DIPEA (3.73 mls, 21.4 mmol) and chloromethyl methyl ether (1.3 ml 17.1 mmol) were added to a solution of compound **96** (1.73 g, 4.3 mmol) in dry dichloromethane (50 ml) at 0°C under an atmosphere of nitrogen. The reaction mixture was removed from the cold bath and allowed to warm to room temperature. After 2 h, TLC analysis indicated that the reaction was complete. Sat. sodium bicarbonate solution (20 ml) was added and the mixture was left stirring for 20 min. The layers were separated and the aqueous phase was extracted with dichloromethane (2x20 ml). The combined organic phases were washed with hydrochloric acid (1M, 2x20 ml), brine (2x20ml), dried over sodium sulfate, and the solvent was removed *in vacuo*. Chromatograhy on silica gel (hexane/ethylacetate, 2:1) afforded compound **98** (1.67 g, 87%) as a colourless oil.
R_f : 0.46 (hexane:ethyl acetate, 1:1). **IR** 1725, 1670 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (3H, s, H18), 1.20 - 2.80 (9H, m), 2.29 (1H, d, J = 16.3 Hz, H3), 2.82 (1H, d, J = 16.3 Hz, H3), 3.16 (1H, d, J = 4.2 Hz, H6), 3.31 (3H, s, 13-$OCH_2OC\underline{H}_3$), 3.42 (4H, s, 19-$CO_2CH_2OC\underline{H}_3$ and H5 overlapped), 3.76 (3H, s, $-CO_2CH_3$), 4.52, 4.76 (2x1H, ABd, J = 7.3 Hz, 13-$OC\underline{H}_2OCH_3$), 5.06 (2H, br s, H17), 5.06, 5.33 (2x1H, ABd, J = 5.9 Hz, 19-$CO_2C\underline{H}_2OCH_3$), 5.92 (1H, br s, H1).
^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1 (C11), 25.1 (C18), 36.3 (C12), 38.7 (C15), 45.3 (14), 47.4 (C9), 48.3 (C8‡), 48.5 (C3), 48.9 (C6), 49.8 (C4‡), 52.1 (C5 and $-CO_2\underline{C}H_3$ overlapped), 55.2 (13-$OCH_2O\underline{C}H_3$), 57.8 (19-$CO_2CH_2O\underline{C}H_3$), 83.8 (C13), 91.3, 91.6

(-O$\underline{C}$H$_2$OCH$_3$), 107.6 (C17), 119.5 (C1), 149.6 (C16), 165.8 (C10), 173.1, 175.1 (C7, C19), 196.5 (C2).

MS (EI) *m/z* 448 (M^+, 5%), 299 (5), 229 (5), 193 (5), 165 (6), 149 (15), 85 (40), 71 (65) 57 (100). **HRMS** (EI) *m/z* calcd for M^+, $C_{24}H_{32}O_8$: 448.2097; found 448.2097.

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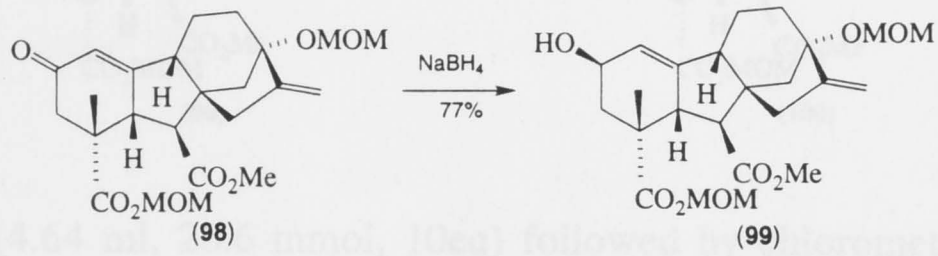
ent-13-Methoxymethoxy-2α-hydroxy-20-norgibberella-1(10),16-diene-7,19-dioic Acid 7-Methyl Ester 19-Methoxymethyl Ester (99)



(98) (99)

Cerium trichloride heptahydrate (2.2 g, 5.9 mmol, 2.5 eq) was added to a solution of the enone **98** (1.05 g, 2.3 mmol) in methanol (30 ml) under an atmosphere of nitrogen. The suspension was stirred for 20 min before being cooled to -78°C. Freshly ground sodium borohydride (133 mg, 3.51 mmol, 1.5 eq) was added and reaction was left to warm up overnight. The reaction mixture was diluted with ethyl acetate (150 ml), acidified with phosphoric acid (10%, 30 ml), the layers separated, and the aqueous phase extracted with ethyl acetate (2x20 ml). The combined organic phases were then washed with brine to pH 5 (3x20 ml), dried over sodium sulfate and the solvent removed *in vacuo*. Chromatograhy on silica gel (hexane/ethyl acetate, 3:1-1:1) afforded the 2β–alcohol **99** (810 mg, 77%) plus small amounts of starting material and the 2α–alcohol.

R_f : 0.36 (hexane:ethyl acetate, 1:1). **IR** 3460, 1735 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (3H, s, H18), 1.37 - 1.98 (6H, m), 1.93 (1H, m, H12), 2.17 (1H, br dd, J_1 = 16.2 Hz, J_2 = 2.4 Hz, H15), 2.47 - 2.64 (3H, m, 1xH3 H9 1xH15), 2.97 (1H, br s, H5), 3.06 (1H, d, J = 4.8 Hz, H6), 3.33 (3H, s, 13-OCH$_2$OC$\underline{H}_3$), 3.47 (3H, s, 19-CO$_2$CH$_2$OC$\underline{H}_3$), 3.71 (3H, s, -CO$_2$CH$_3$), 4.53, 4.77 (2x1H, ABd, J = 7.3 Hz, 13-OC$\underline{H}_2$OCH$_3$), 4.80 (1H, br s, H2), 5.03 (2H, br s, H17), 5.09, 5.32 (2x1H, ABd, J = 5.9Hz, 19-CO$_2$C$\underline{H}_2$OCH3), 5.45 (1H, br s, H1).

^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3 (C11), 26.0 (C18), 36.4 (C12), 38.9 (C15), 44.6, 45.5 (C3, C14), 45.9 (C9), 47.4 (C8), 49.5 (C6), 49.5 (C4), 51.1 (C5), 51.7 (-CO$_2\underline{C}$H$_3$), 55.2 (13-OCH$_2$O$\underline{C}$H$_3$), 57.7 (19-CO$_2$CH$_2$O$\underline{C}$H$_3$), 66.2 (C2), 84.3 (C13), 90.6, 91.5 (19-CO$_2\underline{C}$H$_2$OCH$_3$, 13-O$\underline{C}$H$_2$OCH$_3$), 107.0 (C17), 117.8 (C1), 143.7 (C10), 150.5 (C16), 173.9, 175.9 (C7, C19).

MS (EI) *m/z* 450 (M^+, 1%), 344 (100), 329 (10), 311 (15), 299 (20), 283 (40), 267 (10), 239 (30), 155 (30), 129 (25), 115 (25), 105 (40), 91 (75). **MS** (CI) *m/z* 450 (5),

433 (30), 406 (15), 344 (100), 329 (65), 311 (10), 283 (20), 239 (15). **HRMS** (EI) *m/z* calcd for M^+-CH_2OCH_3, $C_{22}H_{29}O_7$: 405.1913; found 405.1911.

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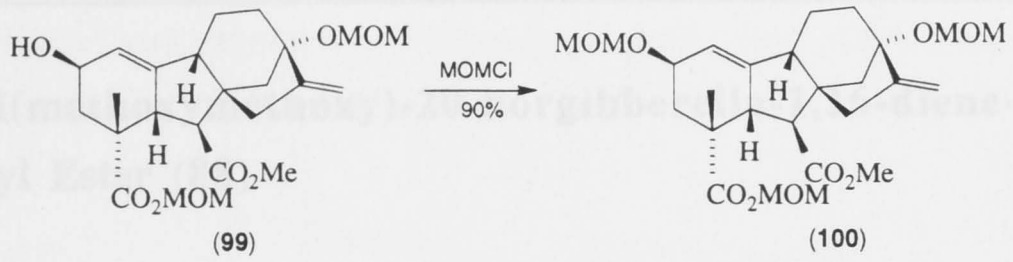
ent-2α,13-Di(methoxymethoxy)-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19-Methoxymethyl Ester (100)



(99) (100)

DIPEA (4.64 ml, 26.6 mmol, 10eq) followed by chloromethyl methyl ether (2.0 ml, 26.6 mmol, 10eq), plus a catalytic amount of DMAP were added to a solution of compound **99** (1.20 g, 2.67 mmol) in dry dichloromethane (30 ml) at 0°C under an atmosphere of nitrogen. The reaction mixture was left to warm to room temperature overnight whereupon TLC analysis indicated that the reaction was complete. Saturated sodium bicarbonate solution (20 ml) was added and the mixture was left stirring for twenty min. The layers were separated and the aqueous phase was extracted with dichloromethane (2x20 ml). The combined organic phases were washed with hydrochloric acid (1M, 2x20 ml), brine (2x20ml), dried over sodium sulfate, filtered, and the solvent was removed *in vacuo*. Chromatograhy on silica gel (hexane/ethyl acetate, 2:1) afforded compound **100** (1.19 g, 90%) as a colourless oil.

R_f : 0.55 (hexane:ethyl acetate, 2:1). **IR** 1765, 1725 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (3H, s, H18), 1.40 (1H, dd, J_1 = 11.0 Hz, J_2 = 2.7 Hz, H14), 1.45 - 1.80 (5H, m), 1.93 (1H, m, J_1 = 13.4 Hz, J_2 = 4.2 Hz, H12), 2.19 (1H, dt, J_1 = 16.6 Hz, J_2 = 2.1 Hz, H15), 2.48 - 2.62 (3H, m, H9 1xH15 1xH3), 2.99 (1H, br s, H5), 3.05 (1H, d, J = 4.7 Hz, H6), 3.33, 3.39 (2x3H, s, $-OCH_2OC\underline{H}_3$), 3.47 (3H, s, 19-$CO_2CH_2OC\underline{H}_3$), 3.71 (3H, s, -$CO_2CH_3$), 4.53, 4.77 (2x1H, ABd, J = 7.4 Hz, 13-$OC\underline{H}_2OCH_3$), 4.71 (1H, m, H2), 4.75 (2H, s, 2-$OC\underline{H}_2OCH_3$), 5.02 (2H, br s, H17), 5.07, 5.34 (2x1H, ABd, J = 6.0 Hz, 19-$CO_2C\underline{H}_2OCH_3$), 5.47 (1H, br s, H1).

^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3 (C11), 26.0 (C18), 36.5 (C12), 38.9 (C15), 41.9 (C3), 45.0 (C14), 46.1 (C9), 47.3 (C8), 49.5 (C4), 49.6, 51.0 (C6, C5), 51.7 (-$CO_2\underline{C}H_3$), 55.2, 55.3 (13-$OCH_2O\underline{C}H_3$, 2-$OCH_2O\underline{C}H_3$), 57.7 (19-$CO_2CH_2O\underline{C}H_3$), 72.8 (C2), 84.3 (C13), 90.7, 91.6, 95.8 (19-$CO_2\underline{C}H_2OCH_3$, 13-$O\underline{C}H_2OCH3$, 2-$O\underline{C}H_2OCH_3$), 106.9 (C17), 115.8 (C1), 144.3 (C10), 150.5 (C16), 173.9, 175.8 (C7, C19).

MS (EI) *m/z* 493 (M^+-H, 1%), 462 (20), 433 (10), 388 (30), 371 (10), 357 (10), 343 (30), 327 (20), 313 (15), 283 (15), 83 (100). **MS** (CI) *m/z* 493 (20), 462 (35), 433 (75), 418 (25), 401 (20), 388 (80), 371 (70), 357 (75), 343 (75), 327 (100), 313 (40), 295 (20), 283 (50). **HRMS** (EI) *m/z* calcd for M^+-CH_3OH, $C_{25}H_{34}O_8$: 462.2254; found 462.2252.

Micro Analysis: $C_{26}H_{38}O_9$ requires C 63.14, H 7.74; found C 62.93, H 8.15.

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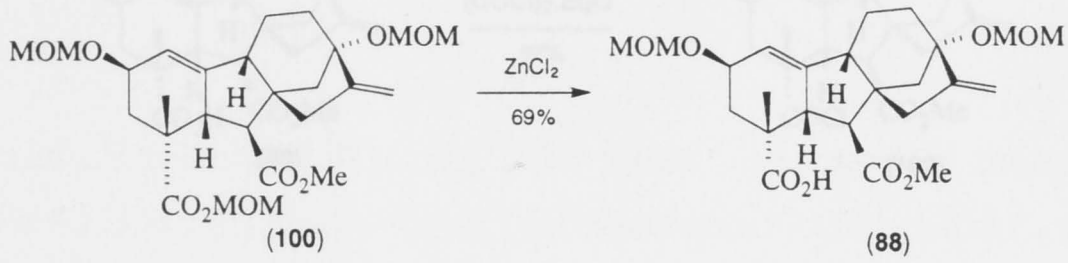
ent-2α,13-Di(methoxymethoxy)-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester (88)



Compound **100** (1.20 g, 2.43 mmol) was heated at reflux in a solution of zinc chloride in methanol (1M, 120 ml) for 10 h. TLC analysis indicated that the reaction was virtually finished, so the solution was concentrated *in vacuo*, taken up in ethyl acetate (50 ml) and washed with sodium dihydrogen phosphate (20%, 2x20 ml) and brine (2x20 ml). The combined aqueous phases were extracted with ethyl acetate (2x20 ml) the organic extracts subsequently washed with brine (10 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate/acetic acid, 3:1:0.1-1:2:0.1) yielded the acid **88** (750 mg, 69%) as an oil, followed by the more polar 13-hydroxy compound **101**. The 13-hydroxy compound **102** was recycled through a protection deprotection sequence to afford the desired acid **88**.

R_f : 0.36 (hexane:ethyl, 2:1). **IR** 1765, 1725 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (3H, s, H18), 1.45 - 1.90 (6H, m), 1.95 (1H, m, H12), 2.14 (1H, br d, J = 16.0 Hz, H15), 2.45 - 2.65 (3H, m, H9 1xH15 1xH3), 2.99 (1H, br s, H5), 3.08 (1H, d, J = 5.0 Hz, H6), 3.35, 3.41 (2x3H, s, $-OCH_2OC\underline{H}_3$), 3.71 (3H, s, $-CO_2CH_3$), 4.57, 4.76 (2x1H, ABd, J = 7.0 Hz, $13-OC\underline{H}_2OCH_3$), 4.68 (1H, m, H2), 4.76 (2H, s, $2-OC\underline{H}_2OCH_3$), 5.03 (2H, br s, H17), 5.46 (1H, br s, H1).

^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3 (C11), 28.1 (C18), 36.6 (C12), 38.9 (C15), 41.7 (C3), 44.6 (C14), 46.1 (C9), 46.6 (C8), 49.5 (C6), 49.7 (C4), 51.0 (C5), 51.7 ($-CO_2\underline{C}H_3$), 55.0, 55.3 ($13-OCH_2O\underline{C}H_3$, $2-OCH_2O\underline{C}H_3$), 72.7 (C2), 84.4 (C13), 91.4, 95.8 ($13-O\underline{C}H_2OCH_3$, $2-O\underline{C}H_2OCH_3$), 106.9 (C17), 115.8 (C1), 144.4 (C10), 150.8 (C16), 176.0 (C19), 179.8 (C7).

MS (EI) *m/z* 418 (M^+-CH_3OH, 20%), 388 (20), 358 (15), 343 (20), 326 (30), 313 (30), 294 (15), 283 (30), 269 (15), 239 (40), 143 (45), 129 (45), 119 (25), 105 (80), 91 (70), 69(80), 55 (100). **MS** (CI) *m/z* 418 (25), 406 (50), 389 (35), 357 (40), 343 (30), 327 (100), 313 (30). **HRMS** (EI) *m/z* calcd for M^+-CH_3OH, $C_{23}H_{30}O_7$: 418.1992; found 418.1990.

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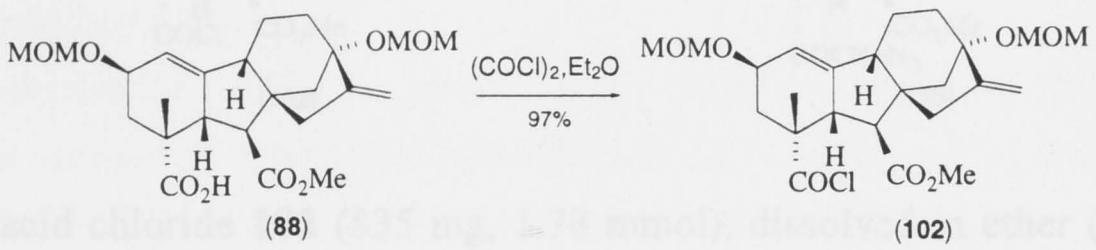
ent-2α,13-Di(methoxymethoxy)-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19-Acyl chloride (102)



(88) (102)

A vigorously stirred solution of oxalyl chloride (1.6 ml, 18.3 mmol, 10eq) in dry ether (30 ml) containing 1 drop of DMF under an atmosphere of nitrogen was cooled to -30°C. The acid **88** (827 mg, 1.83 mmol) was dissolved in dry ether (10 ml) and pyridine (2 ml, large excess) was slowly added *via* a cannula. The solution was then left overnight to warm up to room temperature. The reaction was worked up by filtering through a sintered funnel and washing the solid residue thoroughly with dry ether (5x20 ml). The solvent was removed *in vacuo* and the excess of oxalyl chloride and pyridine were removed by azeotroping with dry benzene (4x30 ml). Finally, filtration through a small plug of Celite followed by removal of the solvent *in vacuo* furnished the desired acid chloride **102** (835 mg, 97%) as a yellow oil.

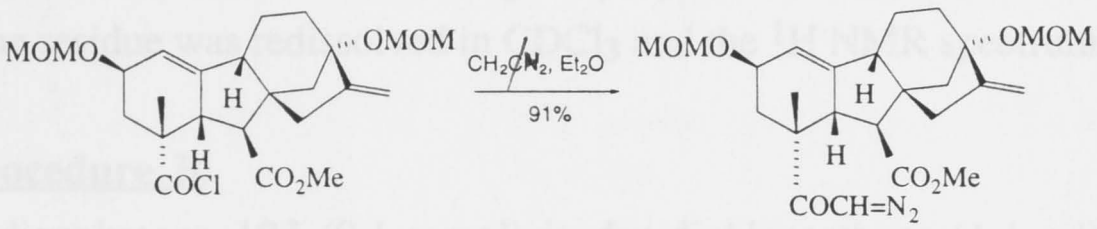
IR 1810, 1770 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (3H, s, H18), 1.50 - 1.90 (6H, m), 1.94 (1H, dd, J_1 = 13.0 Hz, J_2 = 4.8 Hz, H12), 2.17 (1H, br d, J_1 = 16.0 Hz, H15), 2.48 (1H, br d, J = 6.5 Hz, H9), 2.55 (1H, dt, J_1 = 16.0 Hz, J_2 = 2.8 Hz, H15), 2.67 (1H, dd, J = 13.4 Hz, H3), 2.94 (1H, d, J = 5.9 Hz, H6), 3.09 (1H, br s, H5), 3.37, 3.41 (2x3H, s, $-OCH_2OC\underline{H}_3$), 3.71 (3H, s, $-CO_2CH_3$), 4.41 (1H, m, H2), 4.61, 4.81 (2x1H, ABd, J = 7.1 Hz, $13-OC\underline{H}_2OCH_3$), 4.75 (2H, s, $2-OC\underline{H}_2OCH_3$), 5.02 (2H, br s, H17), 5.42 (1H, br s, H1).

^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2 (C11), 25.4 (C18), 36.7 (C12), 39.5 (C15), 42.7 (C3), 45.4 (C14), 46.1 (C9), 49.4 (C6), 50.0 (C8), 51.1 (C5), 51.8 ($-CO_2\underline{C}H_3$), 55.1, 55.3 ($13-OCH_2O\underline{C}H_3$, $2-OCH_2O\underline{C}H_3$), 56.1 (C4), 71.5 (C2), 84.0 (C13), 91.6, 95.7 ($13-O\underline{C}H_2OCH_3$, $2-O\underline{C}H_2OCH_3$), 107.1 (C17), 115.4 (C1), 144.5 (C10), 150.6 (C16), 175.6, 178.1 (C7, C19).

MS (EI) *m/z* 468 (M^+, 1%), 406 (25), 343 (82), 299 (22), 283 (100), 255 (25), 239 (28), 211 (25), 195 (28), 169 (20), 155 (40), 129 (17), 105 (22), 69 (19), 55 (13). **HRMS** (EI) *m/z* calcd for M^+-MeOH, $C_{23}H_{29}O_6{}^{35}Cl$: 436.1653; found 436.1653.

***ent*-2α,13-Di(methoxymethoxy)-19-diazomethyl-19-oxo-20-norgibberella-1(10),16-dien-7-oic Acid 7-Methyl Ester (103)**



The acid chloride **102** (835 mg, 1.78 mmol), dissolved in ether (10 ml), was slowly cannulated into a dried solution of diazomethane in ether (100 ml) at -30°C under an atmosphere of nitrogen. The solution was left to warm up overnight, after which time the reaction was judged to be complete by TLC analysis. The solvent was removed *in vacuo* and the residue was purified on silica gel (hexane/ethyl acetate, 2:1) to yield the diazoketone **103** (774 mg, 91%) as a yellow oil.

R_f : 0.41 (hexane:ethyl acetate, 2:1). **IR** 2105, 1730, 1710 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (3H, s, H18), 1.45 - 1.90 (6H, m), 1.95 (1H, dd, J_1 = 13.2 Hz, J_2 = 5.6 Hz, H12), 2.18 (1H, br d, J_1 = 16.1 Hz, H15), 2.29 (1H, dd, J_1 = 13.6 Hz, J_2 = 6.5 Hz, H3), 2.40 - 2.60 (2H, m, H9 H15), 2.87 (1H, d, J = 5.5 Hz, H6), 2.92 (1H, br s, H5), 3.35, 3.39 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.70 (3H, s, -CO_2CH_3), 4.56, 4.81 (2x1H, ABd, J = 7.1 Hz, 13-$OC\underline{H}_2OCH_3$), 4.67 (1H, m, H2), 4.74 (2H, s, 2-$OC\underline{H}_2OCH_3$), 5.02 (2H, br s, H17), 5.44 (1H, s, -$COCH{=}N_2$), 5.46 (1H, br s, H1).

^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3 (C11), 25.7 (C18), 36.5 (C12), 39.2 (C15), 42.4 (C3), 44.6 (C14), 45.9 (C9), 49.5 (C8‡), 49.8 (C6), 49.9 (C4‡), 51.4 (C5), 51.6 (-$CO_2\underline{C}H_3$), 54.6 (19-$CO\underline{C}H{=}N_2$), 55.1, 55.2 (13-$OCH_2O\underline{C}H_3$, 2-$OCH_2O\underline{C}H_3$), 73.0 (C2), 84.2 (C13), 91.5, 95.7 (13-$O\underline{C}H_2OCH_3$, 2-$O\underline{C}H_2OCH_3$), 106.8 (C17), 115.5 (C1), 144.0 (C10), 150.7 (C16), 175.7 (C7), 196.6 (C19).

MS (EI) *m/z* 446 (M^+-N_2, 1%), 339 (7), 149 (30), 129 (20), 97 (25), 83 (30), 57 (100). **MS** (CI) *m/z* 447(M^++H 30%), 464 (5), 447 (10), 413 (100), 385 (25), 353 (15), 339 (15). **HRMS** (EI) *m/z* calcd for M^+-N_2, $C_{25}H_{34}O_7$: 446.2305; found 446.2305.

CYCLOPROPANATION REACTIONS OF DIAZOKETONE 103

General procedure A

The diazoketone **103** (0.1 mmol) in a mixture of cyclohexane (3.5 ml) and tetrahydrofuran (3.5 ml) was added dropwise to a solution of copper-bronze (121 mg) in cyclohexane (14.3 ml) at reflux under an atmosphere of nitrogen. After 1.5 h, TLC analysis indicated that the reaction was complete. The reaction mixture was diluted with ethyl acetate (15 ml) and filtered through a plug of celite and the solvent removed *in vacuo*. The residue was redissolved in $CDCl_3$ and the ^1H NMR spectrum recorded.

General procedure B

The diazoketone **103** (0.1 mmol) in dry dichloroethane (1.1 ml) was added dropwise to a solution of copper(II)acetylacetonate (2.7 mg, 15 mol%) dissolved in dry dichloroethane (1.75 ml) at reflux, under an atmosphere of nitrogen. After 15 min, TLC analysis indicated that the reaction was complete. The solution was diluted with ethyl acetate (25 ml), washed with ammonia solution (2M, 2x2 ml), and brine (4 ml). The combined aqueous phases were back-extracted with ethyl acetate (2x5 ml). The combined organic phases were dried over sodium sulfate, filtered and the solvent was removed *in vacuo*. The residue was redissolved in $CDCl_3$ and the ^1H NMR spectrum recorded.

General procedure C

The diazoketone **103** (0.1 mmol) in toluene (2.8 ml) was added dropwise to a solution of di-*t*-butylsalicylimidato cuprate (4.2 mg, 10 mol%) dissolved in toluene (5.6 ml) at reflux, under an atmosphere of nitrogen. After 15 min, TLC analysis indicated that the reaction was complete. The solution was diluted with ethyl acetate (20 ml), washed with ammonia solution (2M, 2x4 ml) and brine (5 ml). The combined aqueous phases were back-extracted with ethyl acetate (2x4 ml). The combined organic phases were dried over sodium sulfate, filtered and the solvent was removed *in vacuo*. The residue was redissolved in $CDCl_3$ and the ^1H NMR spectrum recorded.

General procedure D

The diazoketone **103** (0.1 mmol) was dissolved in dichloroethane (1.6 ml) and rhodium acetate (approximately 1.6 mg) dissolved in dichloroethane (1.6 ml) was added. After 15 min, TLC analysis indicated the reaction had finished, so the solvent was then removed *in vacuo*. The residue was redissolved in $CDCl_3$ and the ^1H NMR spectrum recorded.

The results for each experimental procedure used are found in Table 6, with the ^{1}H NMR yield first, followed by the isolated yield for the optimum experiment in parentheses. The isolated yields given are based on the amount of the diazoketone used in the experiment. These general procedures will be used in Chapters 4 and 5 and the same table format applies for those chapters.

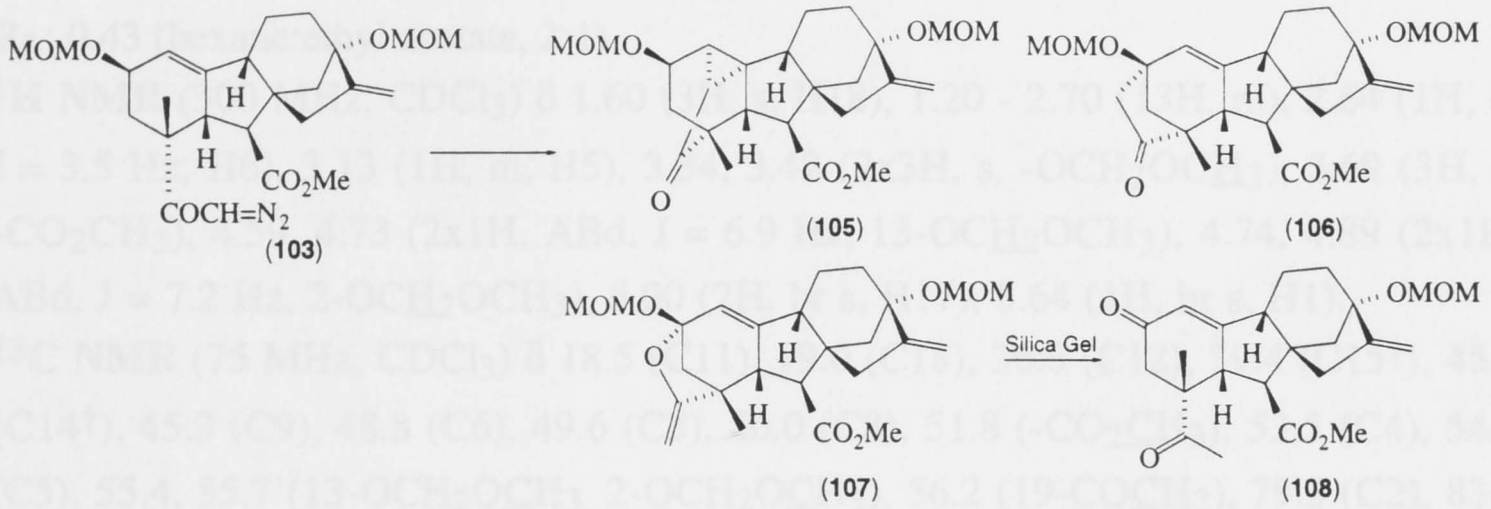
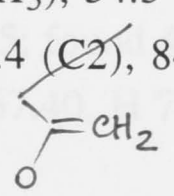


Table 6: Results from Cyclopropanation Reactions.

	^{1}H NMR ratios (isolated yields)			
procedure	**105**	**106**	**107**	**108**
A	46%	38%	15%	
B‡‡	57%, (55%)	18%, (18%)	26%, (5%)	0%, (16%)
C	40%	10%	50%	
D**	5%	75%, (60%)	20%	

‡‡ Purification on silica gel (hexane/ethyl acetate, 3:1) provided four compounds, in order of elution.

***ent*-2α,13-Di(methoxymethoxy)-2β,19-epoxy-19-methylene-20-norgibberella-1(10),16-dien-7-oic Acid 7-Methyl Ester** (**107**, unstable oil††).
R_f : 0.70 (hexane:ethyl acetate, 2:1).
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (3H, s, H18), 1.10 - 2.40 (11H, m), 2.48 (1H, m, H6), 3.14 (1H, m, H5), 3.32, 3.43 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.72 (3H, s, -CO_2CH_3), 3.82, 4.27 (2x1H, br s, 19-O-C=$C\underline{H}_2$), 4.55, 4.78 (2x1H, ABd, J = 6.0 Hz, 13-$OC\underline{H}_2OCH_3$), 4.74, 5.10 (2x1H, ABd, J = 7.0 Hz, 2-$OC\underline{H}_2OCH_3$), 5.02 (2H, br s, H17), 5.71 (1H, br s, H1).
^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5 (C11), 22.0 (C18), 36.6 (C12), 39.5 (C15†), 45.0 (C14†), 47.5 (C8), 48.0 (C3), 49.8 (C4), 50.2 (C6), 51.7 (-$CO_2\underline{C}H_3$), 54.3 (C9), 55.2 (C5), 55.9 (13-$OCH_2O\underline{C}H_3$ and 2-$OCH_2O\underline{C}H_3$ overlapped), 82.4 (C2), 84.1 (C13),



c-2

90.9, 91.9 (13-O$\underline{C}H_2OCH_3$, 2-O$\underline{C}H_2OCH_3$), 106.4, 107.2 (C17, 19-O-C=$\underline{C}H_2$), 120.5 (C1), 146.3, 150.6 (C10, C16), 163.3 (C19), 175.6 (C7).

MS (CI) *m/z* 447(M^++H 23%), 417 (32), 403 (15), 385 (22), 371 (11), 353 (16), 341 (39), 313 (14), 297 (9), 256 (8), 178 (100), 121 (29).

***ent*-2α,13-Di(methoxymethoxy)-19-oxo-2,19-methanogibberella-1(10),16-dien-7-oic Acid 7-Methyl Ester** (**106**, colourless oil).

R_f : 0.43 (hexane:ethyl acetate, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (3H, s, H18), 1.20 - 2.70 (13H, m), 2.64 (1H, d, J = 3.5 Hz, H6), 3.13 (1H, m, H5), 3.34, 3.42 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.69 (3H, s, -CO_2CH_3), 4.59, 4.73 (2x1H, ABd, J = 6.9 Hz, 13-$OC\underline{H}_2OCH_3$), 4.74, 4.89 (2x1H, ABd, J = 7.2 Hz, 2-$OC\underline{H}_2OCH_3$), 5.00 (2H, br s, H17), 5.64 (1H, br s, H1).

^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5 (C11), 19.0 (C18), 36.6 (C12), 39.4 (C15†), 45.2 (C14†), 45.3 (C9), 48.8 (C6), 49.6 (C3), 50.0 (C8), 51.8 (-$CO_2\underline{C}H_3$), 53.5 (C4), 54.2 (C5), 55.4, 55.7 (13-$OCH_2O\underline{C}H_3$, 2-$OCH_2O\underline{C}H_3$), 56.2 (19-$CO\underline{C}H_2$), 79.3 (C2), 83.8 (C13), 91.7, 92.9 (13-O$\underline{C}H_2OCH_3$, 2-O$\underline{C}H_2OCH_3$), 107.4 (C17), 123.0 (C1), 143.5 (C10), 150.4 (C16), 175.5 (C7), 215.8 (C19).

Methyl *ent*-2α,13-di(methoxymethoxy)-19-oxo-1β,20-cyclo-19,20-cyclogibberell-16-en-7-oate (**105**, white crystalline solid).

mp 104.5 - 106°C.

R_f : 0.25 (hexane:ethyl acetate, 2:1). **IR** 1725 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (3H, s, H18), 1.10 - 1.30 (1H, m, H11), 1.30 - 1.50 (1H, m, H11), 1.60 - 1.80 (4H, m, 1xH12 1xH14 1xH15 1xH1), 1.90 - 2.05 (3H, m, 1xH12 1xH14 1xH15), 2.05 - 2.40 (4H, m, 2xH3 1xH20 H9), 2.37 (1H, d, J = 9.9 Hz, H5), 3.00 (1H, d, J = 9.9 Hz, H6), 3.35, 3.37 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.70 (3H, s, -$CO_2C\underline{H}_3$), 4.29 (1H, ddd, J_1 = 8.8 Hz, J_2 = 3.9 Hz, J_3 = 1.9 Hz, H2), 4.53, 4.76 (2x1H, ABd, J = 7.1 Hz, 13-$OC\underline{H}_2OCH_3$), 4.61 (2H, s, 2-$OC\underline{H}_2OCH_3$), 5.05 (1H, br s, H17), 5.13 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8 (C18), 18.3 (C11), 28.8 (C1), 32.1 (C20), 38.0 (C12), 41.6 (C14), 42.8 (C3), 44.6 (C10), 45.0 (C15), 45.7 (C9), 46.1 (C4), 49.3 (C6), 50.3 (C8), 51.7 (-$CO_2\underline{C}H_3$), 52.4 (C5), 55.2, 55.3 (13-$OCH_2O\underline{C}H_3$, 2-$OCH_2O\underline{C}H_3$), 69.7 (C2), 83.3 (C13), 91.6, 95.6 (13-O$\underline{C}H_2OCH_3$, 2-O$\underline{C}H_2OCH_3$), 108.2 (C17), 152.9 (C16), 173.4 (C7), 213.6 (C19).

MS (EI) *m/z* 446 (M^+, 2%), 384 (15), 356 (25), 296 (30), 216 (25), 193 (52), 183 (25), 169 (35), 155 (58), 141 (58), 85 (35), 71 (58), 57 (100). **MS** (CI) *m/z* 447(M^++H 12%), 416 (52), 402 (53), 38)(100), 295 (30), 277 (13), 265 (10), 245 (17), 193 (10). **HRMS** (EI) *m/z* calcd for M^+, $C_{25}H_{34}O_7$: 446.2305; found 446.2305.

Micro Analysis: $C_{25}H_{34}O_7$ requires C 67.24, H 7.67; found C 67.40, H 7.90.

††The acetyl olefin **107** was very unstable and decomposed on silica gel rapidly to form the enone methyl ketone **108**.

Methyl *ent*-13-methoxymethoxy-2,19-dioxo-19-methyl-20-norgibberella-1(10),16-dien-7-oate (**108**, colourless oil).

R_f : 0.15 (hexane:ethyl acetate, 2:1). **IR** 1725, 1700, 1660 cm^{-1}.

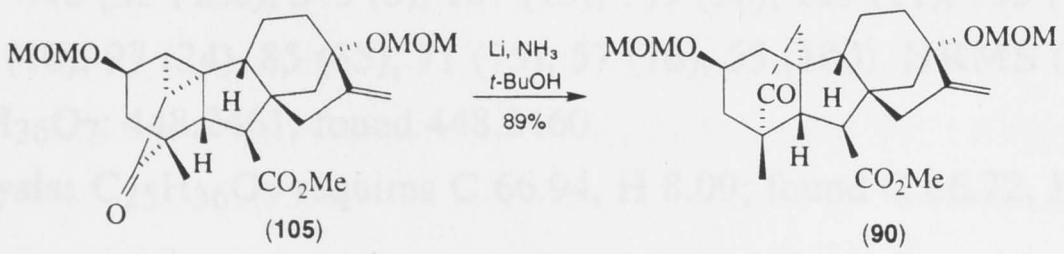
^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (3H, s, H18), 1.20 - 2.60 (8H, m), 2.15 (3H, s, 19-$COCH_3$), 2.40 (1H, d, J = 16.5 Hz, H3), 2.62 (1H, dt, J_1 = 16.0 Hz J_2 = 3.0 Hz, H15), 2.77 (1H, d, J = 16.5 Hz, H3), 3.14 (1H, d, J = 5 Hz, H6), 3.34 (4H, s, -$OCH_2OC\underline{H}_3$, H5 overlapped), 3.75 (3H, s, -CO_2CH_3), 4.58, 4.77 (2x1H, ABd, J = 7.1 Hz, -$OC\underline{H}_2OCH_3$), 5.07 (2H, br s, H17), 5.88 (1H, br s, H1).

^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3 (C11), 25.1 (C18), 29.2 (19-$CO\underline{C}H_3$), 36.4 (C12), 39.3 (C15), 45.5 (C14), 47.5 (C9), 49.0 (C6), 49.3 (C3), 49.9 (C4), 52.0 (-$CO_2\underline{C}H_3$), 52.9 (C5), 52.9 (C8), 55.2 (-$OCH_2O\underline{C}H_3$), 83.7 (C13), 91.6 (-$O\underline{C}H_2OCH_3$), 107.6 (C17), 119.1 (C1), 149.9 (C16), 168.8 (C10), 175.3 (C7), 196.8 (C2), 210.3 (C19).

MS (EI) *m/z* 402 (M^+, 27%), 374 (14), 359 (73), 340 (18), 327 (35), 299 (100), 367 (30), 239 (42), 225 (15), 211 (10), 193 (28), 149 (17), 121 (18) 69 (14). **HRMS** (EI) *m/z* calcd for M^+, $C_{23}H_{30}O_6$: 402.2042; found 402.2044.

The crude mixture of experimental procedure D was also purified on silical gel (hexane/ethyl acetate, 3:1) to provide the C-H insertion product **106 (18 mg, 60%) as a colourless solid.

Methyl *ent*-2α,13-di(methoxymethoxy)-19-oxo-19,20-cyclogibberell-16-en-7-oate (90)



Compound **105** (78 mg, 0.17 mmol) was dissolved in dry THF (5.5 ml) together with *t*-butyl alcohol (44 µl, 0.47 mmol). After cooling to -78°C, liquid ammonia (approximately 20 ml) was distilled into the flask from a sodium amide solution. Lithium metal (approximately 5 mg, 0.72 mmol) was added in small pieces with vigorous stirring and the reaction was quenched with saturated ammonium chloride solution (5 ml) upon appearance of a persistent deep blue colour. The ammonia was allowed to evaporate under a gentle flow of nitrogen. The white solid residue was

dissolved in water (10 ml) and ethyl acetate (50 ml), the layers were separated and the aqueous layer was extracted with ethyl acetate (2x10 ml). The combined organic phases were washed with brine (15 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo* to yield a yellow oil. The residue was dissolved in dichloromethane (10 ml) and treated with Dess-Martin periodinane (151mg, 0.36 mmol, 2eq). After 15 min when TLC analysis indicated that the reaction was complete, saturated sodium bicarbonate solution containing 7% sodium thiosulphate (20 ml) was added and reaction mixture left stirring until cloudiness had dissipated. The reaction mixture was diluted with ethyl acetate (60 ml) and the organic phase washed with sat. sodium bicarbonate (10 ml), then with brine (10 ml). The combined aqueous phases were extracted with ethyl acetate (2x20 ml). The combined organic phases were dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 2:1) afforded the cyclopentanone **90** (69.6 mg, 89%) as a white crystalline solid.

mp 106 - 107°C.

R_f : 0.61 (hexane:ethyl acetate, 1:1). **IR** 1735 cm^{-1}.

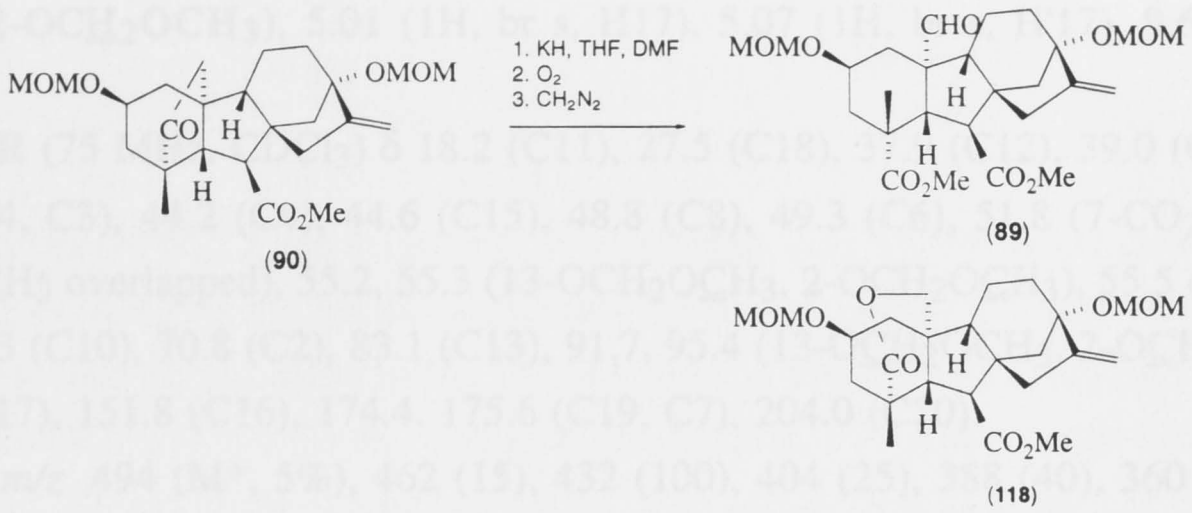
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (3H, s, H18), 1.20 - 2.35 (15H, m), 2.39 (1H, d, J = 12.0 Hz, H5), 2.51 (1H, d, J = 12.0 Hz, H6), 3.31, 3.36 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.69 (3H, s, -CO_2CH_3), 3.69 (1H, m, H2), 4.55, 4.73 (2x1H, ABd, J = 7.1 Hz, 13-$OC\underline{H}_2OCH_3$), 4.58 (2H, s, 2-$OC\underline{H}_2OCH_3$), 5.00 (1H, br s, H17), 5.14 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9 (C18), 18.9 (C11), 38.3 (C12), 40.3 (C20), 43.2, 43.7 (C14, C1), 44.4, 44.7 (C15, C3), 49.2, 49.4 (C10, C4), 51.4 (C6), 51.9 (-$CO_2\underline{C}H_3$), 52.7 (C8), 53.8 (C9), 55.3 (2-$OCH_2O\underline{C}H_3$, 13-$OCH_2O\underline{C}H_3$ overlapped), 59.2 (C5), 71.3 (C2), 83.5 (C13), 92.0, 95.2 (13-$O\underline{C}H_2OCH_3$, 2-$O\underline{C}H_2OCH_3$), 107.9 (C17), 154.0 (C16), 173.2 (C7), 218.2 (C19).

MS (EI) *m/z* 448 (M^+, 2%), 345 (3), 167 (15), 149 (56), 129 (11), 113 (18), 111 (11), 105 (10), 98 (10), 97 (24), 85 (35), 71 (75), 57 (76), 55 (100). **HRMS** (EI) *m/z* calcd for M^+, $C_{25}H_{36}O_7$: 448.2461; found 448.2460.

Micro Analysis: $C_{25}H_{36}O_7$ requires C 66.94, H 8.09; found C 66.72, H 8.39.

Dimethyl *ent*-2α,13-di(methoxymethoxy)-20-oxo-gibberell-16-en-7,19-dioate (**89**) and ***ent*-2α,13-Di(methoxymethoxy)-20-hydroxy-gibberell-16-en-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone** (**118**).



An excess of dry (oil free) potassium hydride (approximately 170 mg, 4.24 mmol) was added to a solution of the cyclopentanone **90** (170 mg, 0.38 mmol) in dry THF (10 ml) and dry DMF (10 ml) at 0°C with vigorously stirring under an atmosphere of nitrogen. The reaction was left stirring for 2 h, after which time the reaction flask was thoroughly flushed with nitrogen before a steady stream of dry oxygen gas was passed through the solution. After 20 min TLC analysis indicated that the reaction was complete. The reaction was carefully quenched with methanol (5 ml) and the solvent removed *in vacuo*. The DMF was removed under high vacuum with gentle heating. The solid residue was dissolved in water (20 ml) and ethyl acetate (50 ml), the layers were separated and the aqueous phase was extracted with ethyl acetate (2x20 ml). The combined organic phases were washed with brine (10 ml), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. The residue was dissolved in methanol (10 ml) and treated with an excess of diazomethane. The solvent was removed under a gentle stream of nitrogen. Purification on silica gel (hexane/ethyl acetate, 3:1) afforded the desired aldehyde **89** (164 mg, 88%) as a colourless oil.

When this reaction was repeated with cyclopentanone **90** (150 mg, 0.33 mmol) and a large excess of potassium hydride, wet oxygen was inadvertently used, this generated heat in the reaction mixture. After work-up, a mixture of the aldehyde **89** (60 mg, 36%) and the lactone **118** (75 mg, 48%) were obtained (overall a 85% yield). A number of experiments were attempted to repeat this result, but none succeeded.

Dimethyl *ent*-2α,13-di(methoxymethoxy)-20-oxo-gibberell-16-en-7,19-dioate (**89**).

R_f : 0.72 (hexane:ethyl acetate, 1:1). **IR** 1725 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (1H, t, J = 11.3 Hz, H1β), 1.15 (3H, s, H18), 1.17 (1H, m, H3β), 1.40 - 1.80 (5H, m), 1.90 (1H, m, H12), 2.00 - 2.30 (3H, m,

1xH14 2xH15), 2.26 (1H, d, J = 12.4 Hz, H5), 2.45 (1H, dd, J_1 = 13.2 Hz, J_2 = 1.4 Hz, H3α), 2.68 (1H, dd, J_1 = 12.1 Hz, J_2 = 1.3 Hz, H1α), 3.35, 3.36 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.65, 3.74 (2x3H, s, -CO_2CH_3), 3.80 (1H, d, J = 12.4 Hz, H6), 3.86 (1H, m, H2), 4.53, 4.76 (2x1H, ABd, J = 7.3 Hz, 13-$OC\underline{H}_2OCH_3$), 4.68 (2H, s, 2-$OC\underline{H}_2OCH_3$), 5.01 (1H, br s, H17), 5.07 (1H, br s, H'17), 9.66 (1H, s, H20).

^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2 (C11), 27.5 (C18), 37.9 (C12), 39.0 (C1), 43.3, 43.7 (C14, C3), 44.2 (C4), 44.6 (C15), 48.8 (C8), 49.3 (C6), 51.8 (7-$CO_2\underline{C}H_3$ and 19-$CO_2\underline{C}H_3$ overlapped), 55.2, 55.3 (13-$OCH_2O\underline{C}H_3$, 2-$OCH_2O\underline{C}H_3$), 55.5 (C9), 56.1 (C5), 60.3 (C10), 70.8 (C2), 83.1 (C13), 91.7, 95.4 (13-$O\underline{C}H_2OCH_3$, 2-$O\underline{C}H_2OCH_3$), 107.5 (C17), 151.8 (C16), 174.4, 175.6 (C19, C7), 204.0 (C20).

MS (EI) *m/z* 494 (M^+, 5%), 462 (15), 432 (100), 404 (25), 388 (40), 360 (60), 344 (53), 299 (35), 253 (30), 267 (21), 251 (20), 211 (25), 179 (23), 143 (20) 105 (20).

HRMS (EI) *m/z* calcd for M^+, $C_{26}H_{38}O_9$: 494.2516; found 494.2514.

Micro Analysis: $C_{26}H_{38}O_9$ requires C 63.14, H 7.74; found C 63.41, H 8.08.

***ent*-2α,13-Di(methoxymethoxy)-20-hydroxy-gibberell-16-en-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (118).**

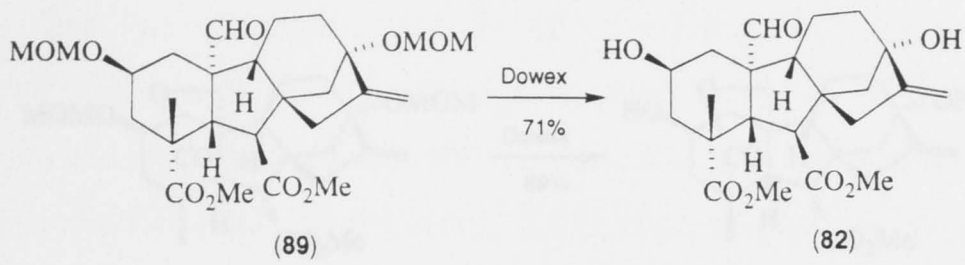
R_f : 0.49 (hexane:ethyl acetate, 1:1). **IR** 1730 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (3H, s, H18), 1.20 - 2.40 (13H, m), 2.28 (1H, d, J = 12.6 Hz, H5), 2.75 (1H, d, J = 12.6 Hz, H6), 3.32, 3.36 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.70 (3H, s, -CO_2CH_3), 3.70 (1H, m, H2), 4.12 (1H, d, J_{gem} = 12.1 Hz, 20-pro-S-H), 4.37 (1H, dd, J_{gem} = 12.1 Hz, $J_{20R,1\beta}$ = 2.0 Hz, 20-pro-R-H), 4.53, 4.73 (2x1H, ABd, J = 7.2 Hz, 13-$OC\underline{H}_2OCH_3$), 4.62 (2H, s, 2-$OC\underline{H}_2OCH_3$), 4.98 (1H, br s, H17), 5.11 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5 (C11), 22.9 (C18), 37.8 (C12), 40.5 (C1), 41.6 (C3 and C14 overlapped), 42.2 (C10), 44.7 (C15), 45.3 (C4), 48.2 (C8), 50.8 (C6), 52.7 (-$CO_2\underline{C}H_3$), 54.7 (C5), 55.3 (C9), 55.3 (13-$OCH_2O\underline{C}H_3$ and 2-$OCH_2O\underline{C}H_3$ overlapped), 71.2 (C2), 73.9 (C20), 83.5 (C13), 91.9, 95.3 (13-$O\underline{C}H_2OCH_3$, 2-$O\underline{C}H_2OCH_3$), 107.6 (C17), 153.1 (C16), 172.9 (C19), 174.1 (C7).

MS (EI) *m/z* 464 (M^+, 70%), 449 (20), 433 (45), 419 (22), 402 (80), 391 (50), 375 (90), 361 (92), 342 (45), 330 (100), 312 (80), 298 (55), 179 (80). **HRMS** (EI) *m/z* calcd for M^+, $C_{25}H_{36}O_8$: 464.2410; found 464.2412.

Dimethyl *ent*-2α,13-dihydroxy-20-oxo-gibberell-16-en-7,19-dioate (82)



(89) (82)

Dowex 50W-X2 resin (80 mg of wet resin) was added to a solution of the aldehyde **89** (14 mg, 0.028 mmol) in methanol (3 ml) and water (0.5 ml). The reaction mixture was then heated under reflux for 14 h, after which time TLC analysis indicated that the reaction was complete. The reaction mixture was diluted with ethyl acetate (50 ml) and filtered through a pad of celite. The filtrate was then washed with brine (10 ml), dried over sodium sulfate and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 2:1-1:2) afforded the desired deprotected aldehyde **82** (8.3 mg, 71%) mixed with an impurity (approximately 10%) that could not be separated by chromatography.

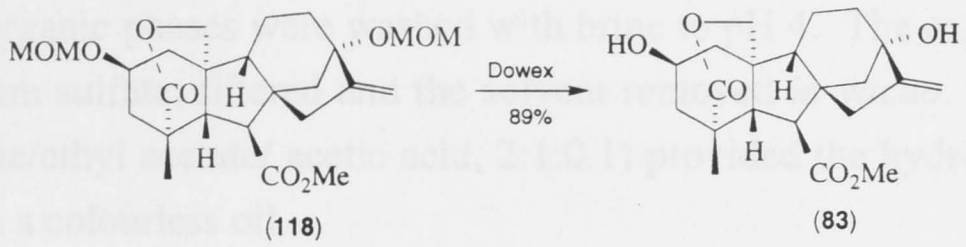
R_f : 0.12 (hexane:ethyl acetate, 1:1.5).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (1H, m, J = 11.1 Hz, H1β), 1.17 (3H, s, H18), 1.22 (1H, m, H3β), 1.50 - 1.90 (10H, m), 2.67 (1H, m, H14), 2.31 (1H, d, J = 12.5 Hz, H5), 2.40 (1H, ddd, J_1 = 12.9 Hz, J_2 = 4.4 Hz, J_3 = 1.6 HZ, H3α), 2.62 (1H, ddd, J_1 = 12.0 Hz, J_2 = 4.7 Hz, J_3 = 1.7 Hz, H1α), 3.65, 3.75 (2x3H, s, $-CO_2CH_3$), 3.83 (1H, d, J = 12.5 Hz, H6), 4.00 (1H, m, H2), 4.95 (1H, br s, H17), 5.19 (1H, br s, H'17), 9.66 (1H, s, H20).

^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7 (C11), 27.7 (C18), 38.3 (C12), 41.3 (C1), 44.2, 44.4 (C14, C3), 46.1 (C15), 46.7 (C4), 48.9 (C8), 49.3 (C6), 51.9 (7-$CO_2\underline{C}H_3$ and 19-$CO_2\underline{C}H_3$ overlapped), 55.5, 55.9 (C9, C5), 60.7 (C10), 64.9 (C2), 78.2 (C13), 106.6 (C17), 155.7 (C16), 174.4 and 175.9 (C19 and C7), 204.2 (C20).

MS (EI) *m/z* 374 (M^+, 100%), 356 (20), 342 (40), 328 (90), 314 (14), 300 (70), 269 (40), 135 (70), 105 (40), 91 (45). **HRMS** (EI) *m/z* calcd for M^+-CH_3OH, $C_{21}H_{26}O_6$: 374.1729; found 374.1729.

ent-2α,13,20-Trihydroxy-gibberell-16-en-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (83)



(118) (83)

Dowex 50W-X2 resin (80 mg of wet resin) was added to a solution of the lactone **118** (11 mg, 0.023 mmol) in methanol (3 ml) and water (0.5 ml). The reaction mixture was then heated under reflux for 14 h, after which time TLC analysis indicated that the reaction was complete. The reaction was diluted with ethyl acetate (50 ml) and filtered through a pad of celite. The filtrate was then washed with brine (10 ml), dried over sodium sulfate and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 2:1 - 1:2) afforded the desired deprotected lactone **83** (8.0 mg, 89%) as an off-white solid.

R_f : 0.21 (hexane:ethyl acetate, 1:3). **IR** 1730 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (3H, s, H18), 1.20 - 2.80 (16H, m), 2.20 (1H, d, J = 12.6 Hz, H5), 2.76 (1H, d, J = 12.6 Hz, H6), 3.71 (3H, s, $-CO_2CH_3$), 4.04 (1H, m, H2), 4.11 (1H, d, J_{gem} = 12.3 Hz, 20-pro-S-H), 4.38 (1H, dd, J_{gem} = 12.3 Hz, $J_{20,1\beta}$ = 2.4 Hz, 20-pro-R-H), 4.92 (1H, br s, H17), 5.23 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8 (C11), 23.0 (C18), 38.0 (C12), 41.7 (C1), 42.5 (C10), 44.6, 44.7 (C14, C3), 46.9, 47.8 (C4, C8), 48.5 (C15), 50.8 (C6), 52.0 ($-CO_2\underline{C}H_3$), 52.6 (C5), 54.8 (C9), 65.5 (C2), 74.0 (C20), 78.5 (C13), 106.6 (C17), 156.8 (C16), 173.0, 174.4 (C19, C7).

MS (EI) *m/z* 376 (M^+, 90%), 344 (55), 316 (30), 298 (100), 280 (25), 271 (30), 253 (87), 135 (60). **HRMS** (EI) *m/z* calcd for M^+, $C_{21}H_{28}O_6$: 376.1886; found 376.1887.

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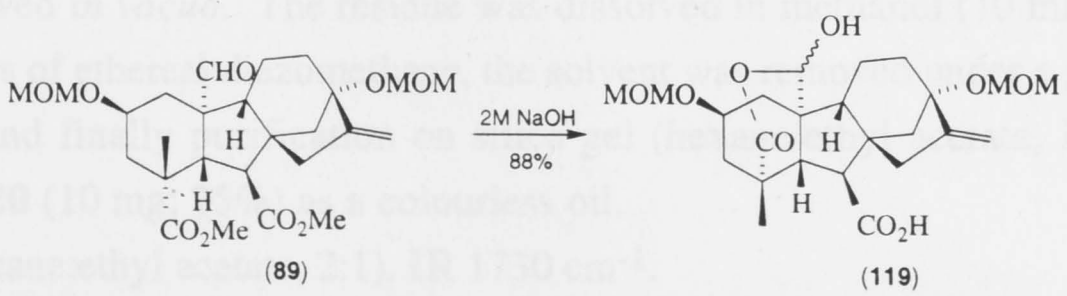
ent-20,20-Dihydroxy-2α,13-di(methoxymethoxy)gibberell-16-ene-7,19-dioic Acid 19,20-Lactone (119)



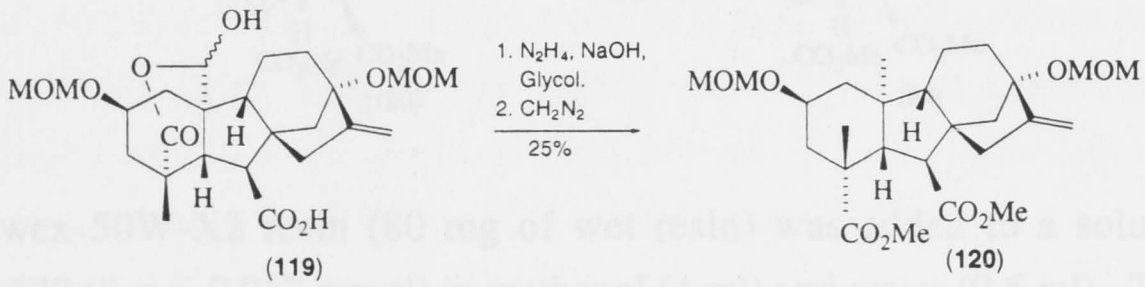
(89) (119)

The aldehyde **89** (96 mg, 0.19 mmol) was dissolved in methanol (1 ml) and sodium hydroxide solution (2M, 3 ml). The reaction mixture was heated at reflux for

24 h. After cooling the mixture was diluted with ethyl acetate containing 20% 2-butanol (50 ml) and was acidified with phosphoric acid (10%, 10 ml). The layers were separated and the aqueous phase was extracted with the ethyl acetate/2-butanol mixture (2x20 ml). The combined organic phases were washed with brine to pH 4. The organic phase was dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Purification on silica gel (hexane/ethyl acetate/ acetic acid, 2:1:0.1) provided the hydroxy lactone **119** (80 mg, 88%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (3H, s, H18), 1.20 - 2.80 (17H, m), 3.36 (4H, s, 13-$OCH_2OC\underline{H}_3$[#] and H6 overlapped), 3.39 (3H, s, 2-$OCH_2OC\underline{H}_3$[#]), 3.90 (1H, m, H2), 4.57, 4.78 (2x1H, ABd, J = 7.3 Hz, 13-$OC\underline{H}_2OCH_3$[†]), 4.64, 4.66 (2x1H, ABd, J = 6.8 Hz, 2-$OC\underline{H}_2OCH_3$[†]), 5.00 (1H, br s, H17), 5.11 (1H, br s, H'17), (H20 not observed).

Dimethyl *ent*-2α,13-di(methoxymethoxy)gibberell-16-en-7,19-dioate (120)



(119) (120)

Anhydrous hydrazine (0.25 ml) was added to a solution of the hydroxy lactone **119** (38 mg, 0.081 mmol) in ethylene glycol (2 ml) and the reaction mixture was heated at 100°C for 30 min. Half a pellet of sodium hydroxide (approximately 200 mg) was added and the temperature was raised to 116°C for 1 h. Finally, the temperature was raised to 180°C and the reaction continued overnight. After cooling the mixture was diluted with ethyl acetate/ 20% 2-butanol (50 ml) and was acidified with phosphoric acid (10 %, 10 ml). The layers were separated and the aqueous phase was extracted with the ethyl acetate/ 2-butanol mixture (2x20 ml). The combined organic phases were washed with brine to pH 4. The organic phase was dried over sodium sulfate, filtered and the solvent removed *in vacuo*. The residue was dissolved in methanol (10 ml) and treated with an excess of ethereal diazomethane, the solvent was removed under a gentle stream of nitrogen and finally purification on silica gel (hexane/ethyl acetate, 3:1) afforded compound **120** (10 mg, 25%) as a colourless oil.

R_f : 0.65 (hexane:ethyl acetate, 2:1). **IR** 1730 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.71 (3H, s, H20), 1.12 (3H, s, H18), 0.80 - 2.40 (13H, m), 1.98 (1H, d, J = 12.3 Hz, H5), 2.51 (1H, ddd, J_1 = 13.1 Hz, J_2 = 3.2 Hz, J_3 = 1.4 Hz, H3α), 3.33 (1H, d, J = 12.3 Hz, H6), 3.36, 3.37 (2x3H, s,

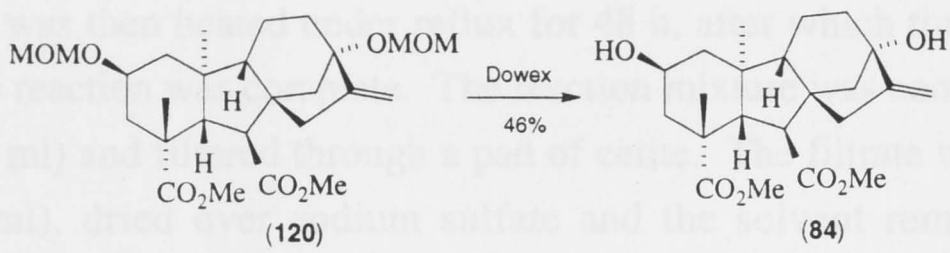
-$OCH_2OC\underline{H}_3$), 3.68, 3.76 (2x3H, s, -CO_2CH_3), 4.20 (1H, m, H2), 4.56, 4.76 (2x1H, ABd, J = 7.1 Hz, 13-$OC\underline{H}_2OCH_3$), 4.66, 4.70 (2x1H, ABd, J = 6.8 Hz, 2-$OC\underline{H}_2OCH_3$), 4.99 (1H, br s, H17), 5.06 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7 (C20), 17.9 (C11), 28.3 (C18), 38.4 (C12), 44.0, (C10), 44.1 (C14), 44.8 (C4 and C1 overlapped), 45.3, 45.7 (C15, C3), 48.7 (C8), 50.1 (C6), 51.6, 51.7 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 55.3, 55.4 (13-$OCH_2OC\underline{H}_3$, 2-$OCH_2OC\underline{H}_3$), 55.7 (C9), 57.2 (C5), 71.0 (C2), 83.7 (C13), 91.9, 95.2 (13-$O\underline{C}H_2OCH_3$, 2-$O\underline{C}H_2OCH_3$), 107.1 (C17), 152.5 (C16), 175.3, 177.0 (C19, C7).

MS (EI) *m/z* 480 (M^+, 8%), 448 (32), 418 (30), 389 (55), 358 (59), 343 (55), 327 (25), 313 (35), 299 (52), 239 (52), 179 (57), 149 (42), 85 (55), 71 (65), 59 (100).

HRMS (EI) *m/z* calcd for M^+, $C_{26}H_{40}O_8$: 480.2723; found 480.2723.

Dimethyl *ent*-2α,13-dihydroxy-gibberell-16-en-7,19-dioate (84)



(120) (84)

Dowex 50W-X2 resin (80 mg of wet resin) was added to a solution of the compound **120** (8 mg, 0.017 mmol) in methanol (4 ml) and water (0.5 ml). The reaction mixture was then heated under reflux for 10 h, cooled, then diluted with ethyl acetate (50 ml) and filtered through a pad of celite. The filtrate was then washed with brine (10 ml), dried over sodium sulfate and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 3:1-1:2) afforded compound **84** (3.0 mg 46%) as a white solid, plus some 2-methoxymethoxy,13-hydroxy compound **121** (2 mg, 30%).

R_f : 0.24 (hexane:ethyl acetate, 1:1).

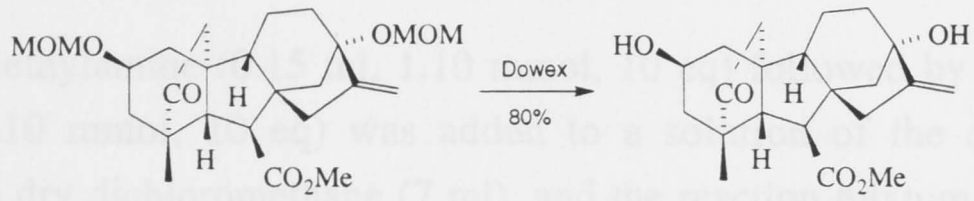
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.71 (3H, s, H20), 1.14 (3H, s, H18), 0.80 - 2.40 (14H, m), 1.99 (1H, d, J = 12.5 Hz, H5), 2.48 (1H, m, H3), 3.32 (1H, d, J = 12.5 Hz, H6), 3.67, 3.71 (2x3H, s, -CO_2CH_3), 4.16 (1H, m, H2), 4.93 (1H, br s, H17), 5.15 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 15.8 (C20), 18.1 (C11), 28.5 (C18), 38.7 (C12), 44.2, (C10), 44.7 (C14), 45.0 (C4), 46.7 (C15), 47.5, 48.2 (C3, C1), 48.6 (C8), 50.1 (C6), 51.6, 51.7 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 55.8 (C9), 56.9 (C5), 65.2 (C2), 78.6 (C13), 106.0 (C17), 156.4 (C16), 175.2, 177.0 (C19, C7).

MS (EI) *m/z* 360 (M^+- CH_3OH, 42%), 332 (19), 314 (100), 299 (51), 288 (16), 273 (24), 255 (45), 239 (25). **HRMS** (EI) *m/z* calcd for M^+- CH_3OH, $C_{21}H_{28}O_5$: 360.1937; found 360.1936.

8.4.2 2β–HYDROXY, 13-DEOXY SERIES

Methyl *ent*-2α,13-dihydroxy-19-oxo-19,20-cyclogibberell-16-en-7-oate (**91**)



(**90**) (**91**)

Dowex 50W-X2 resin (290 mg of wet resin) was added to a solution of the cyclopentanone **90** (49 mg, 0.11 mmol) in methanol (17.1 ml) and water (2.83 ml). The reaction mixture was then heated under reflux for 48 h, after which time TLC analysis indicated that the reaction was complete. The reaction mixture was cooled, diluted with ethyl acetate (50 ml) and filtered through a pad of celite. The filtrate was then washed with brine (10 ml), dried over sodium sulfate and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 2:1-1:2) afforded the desired dihydroxycyclopentanone **91** (31.5 mg 80%) as a slightly off white solid.

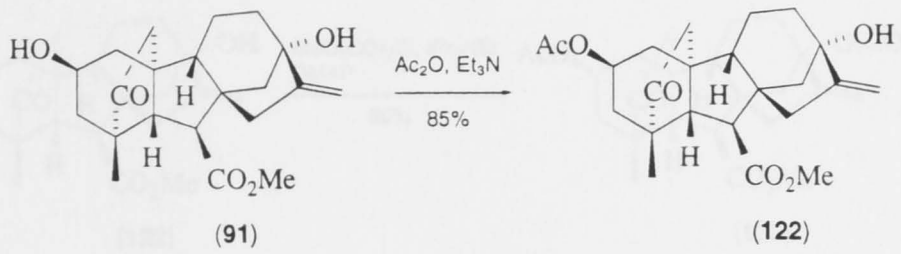
R_f : 0.28 (hexane:ethyl acetate, 1:3). **IR** 1740 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, s, H18), 0.80 - 2.30 (17H, m), 2.40 (1H, d, J = 12.0 Hz, H5), 2.52 (1H, d, J = 12.0 Hz, H6), 3.70 (3H, s, $-CO_2CH_3$), 3.86 (1H, 7 line multiplet, J (apparent) = ca. 5.5 Hz, H2), 4.94 (1H, br s, H17), 5.25 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8 (C18), 19.9 (C11), 38.5 (C12), 43.9, 44.0, 44.1 (C20, C14, C1), 45.4 (C15), 47.0 (C3), 49.4, 49.6 (C10, C4), 51.2 (C6), 51.9 ($-CO_2\underline{C}H_3$), 52.9 (C8), 53.7 (C9), 59.2 (C5), 65.8 (C2), 78.4 (C13), 106.9 (C17), 157.6 (C16), 173.2 (C7), 218.5 (C19).

MS (EI) *m/z* 360 (M^+, 100%), 328 (53), 301 (69), 241 (36), 157 (22), 135 (68), 121 (31), 105 (38), 91 (55), 69 (42), 55 (55). **HRMS** (EI) *m/z* calcd for M^+, $C_{21}H_{28}O_5$: 360.1937; found 360.1936.

Methyl *ent*-2α-acetoxy-13-hydroxy-19-oxo-19,20-cyclogibberell-16-en-7-oate (122)



(91) (122)

Dry triethylamine (0.15 ml, 1.10 mmol, 10 eq) followed by acetic anhydride (0.104 ml, 1.10 mmol, 10 eq) was added to a solution of the diol **91** (50 mg, 0.11 mmol) in dry dichloromethane (7 ml), and the reaction mixture was left stirring. After 24 h, TLC analysis indicated that the reaction was complete. Ice was added to quench the reaction. After stirring for 10 min, the reaction mixture was diluted with ethyl acetate (50 ml) and acidified with sodium dihydrogen phosphate solution (20%, 25 ml), the layers were separated and the aqueous phase was extracted with ethyl acetate (2x10 ml). The combined organic phases were washed with brine (3x10 ml) to pH 4, dried over sodium sulfate and the solvent removed *in vacuo*, to yield the mono acetate **122** (47 mg, 85% crude). It was found that it was best to use the monoacetate without further purification due to losses of the product on silica gel. A small amount was purified for characterization. Chromatography on silica gel (hexane/ethyl acetate, 1:2) afforded the desired monoacetate **122** as an off-white solid.

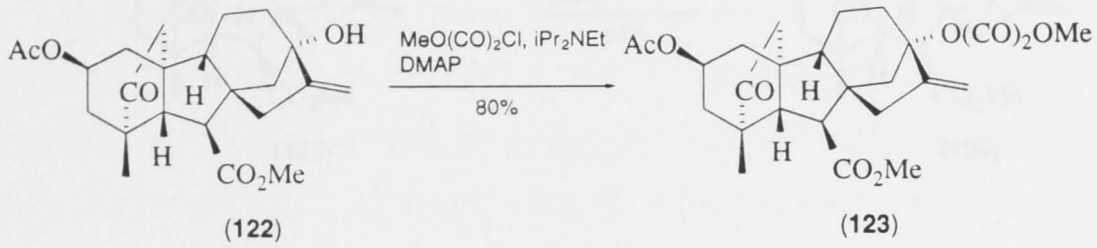
R_f : 0.60 (hexane:ethyl acetate, 1:3). **IR** 1735 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, s, H18), 1.20 - 2.40 (16H, m), 2.00 (3H, s, $-COCH_3$), 2.40 (1H, d, J = 12.0 Hz, H5), 2.54 (1H, d, J = 12.0 Hz, H6), 3.70 (3H, s, $-CO_2CH_3$), 4.88 (1H, m, H2), 4.93 (1H, br s, H17), 5.25 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8 (C18), 19.9 (C11), 21.0 ($-CO\underline{C}H_3$), 38.5 (C12), 41.7 (CH_2), 42.6 (CH_2), 43.3 (CH_2), 44.0 (CH_2), 44.4 (CH_2), 49.2, 49.5 (C10, C4), 51.2 (C6), 51.9 ($-CO_2\underline{C}H_3$), 52.9 (C8), 53.8 (C9), 59.0 (C5), 68.2 (C2), 78.3 (C13), 106.8 (C17), 157.6 (C16), 170.2 ($-\underline{C}OCH_3$), 173.0 (C7), 217.4 (C19).

MS (EI) *m/z* 402 (M^+, 5%), 371 (13), 356 (6), 342 (100), 310 (90), 300 (98), 282 (52), 253 (25), 241 (39), 157 (18), 135 (45), 121 (24), 105 (34), 91 (35), 78 (21), 55 (27). **HRMS** (EI) *m/z* calcd for M^+, $C_{23}H_{30}O_6$: 402.2042; found 402.2041.

Methyl *ent*-2α-acetoxy-13-methyloxalyloxy-19-oxo-19,20-cyclogibberell-16-en-7-oate (123)



(122) (123)

DIPEA (68 µl, 0.39 mmol, 6 eq), plus a catalytic amount of DMAP, followed by methyloxalyl chloride (35 µl, 0.39 mmol, 6 eq) were added to a solution of the monoacetate **122** (26. mg, 0.065 mmol) in dry dichloromethane (7 ml) and the reaction mixture was left stirring. After 24 h, TLC analysis indicated that the reaction was complete. The reaction mixture was diluted with ethyl acetate (50 ml) and washed with sat. sodium bicarbonate solution (15 ml) and brine (15 ml). The combined aqueous phases were back-extracted with ethyl acetate (2x10 ml). The combined organic phases were dried over sodium sulfate, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 2:1) afforded compound **123** (24.6 mg, 80%) as a colourless oil.

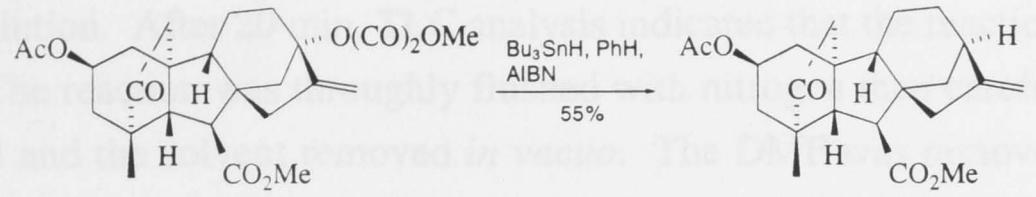
R_f : 0.86 (hexane:ethyl acetate, 1:2). **IR** 1770, 1745, 1740 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, s, H18), 1.20 - 2.50 (15H, m), 2.00 (3H, s, $-COCH_3$), 2.41 (1H, d, J = 11.9 Hz, H5), 2.55 (1H, d, J = 11.9 Hz, H6), 3.69 (3H, s, $-CO_2CH_3$), 3.88 (3H, s, $-(CO)_2-OCH_3$), 4.88 (1H, 7-line multiplet, H2), 5.06 (1H, br s, H17), 5.26 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8 (C18), 19.7 (C11), 21.1 ($-CO\underline{C}H_3$), 36.2 (C12), 39.3 (C20), 41.7 (CH_2), 42.6 (CH_2), 43.2 (CH_2), 43.3 (CH_2), 49.1 (C10), 50.4 (C4), 50.8 (C9), 52.0 ($-CO_2\underline{C}H_3$), 52.8 (C8), 53.4 (C6), 53.5 ($-(CO)_2-O\underline{C}H_3$), 58.9 (C5), 68.1 (C2), 87.5 (C13), 109.1 (C17), 152.1 (C16), 156.3, 158.3 ($-(\underline{C}O)_2-CH_3$), 170.2 ($-\underline{C}OCH_3$), 172.7 (C7), 217.0 (C19).

MS (EI) *m/z* 488 (M^+, 2%), 457 (11), 428 (43), 396 (68), 368 (10), 324 (100), 282 (33), 265 (30), 237 (16), 223 (35), 181 (15), 129 (15), 94 (24). **HRMS** (EI) *m/z* calcd for M^+, $C_{26}H_{32}O_9$: 488.2046; found 488.2046.

Methyl *ent*-2α-acetoxy-19-oxo-19,20-cyclogibberell-16-en-7-oate (124)



(123) (124)

Methyloxalyl ester **123** (50 mg, 0.10 mmol) was dissolved in dry benzene (5 ml) under a nitrogen atmosphere. Tributyltin hydride (75 µl, 0.3 mmol, 3 eq) was added and the reaction mixture was heated at reflux. The reaction mixture was maintained at this temperature while catalytic amounts of AIBN were added at 30 min intervals. After 2 h, TLC analysis indicated that the reaction was complete. The solvent was removed *in vacuo* and after iterative chromatography on silica gel (hexane/ethyl acetate, 5:1) compound **124** (21.7 mg, 55%) was obtained as a colourless oil.

R_f : 0.81 (hexane:ethyl acetate, 3:1). **IR** 1735 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (3H, s, H18), 1.10 - 2.40 (15H, m), 2.00 (3H, s, $-COCH_3$), 2.39 (1H, d, J = 11.9 Hz, H5), 2.51 (1H, d, J = 11.9 Hz, H6), 2.62 (1H, m, H13), 3.68 (3H, s, $-CO_2CH_3$), 4.84 (1H, s, H17), 4.89 (1H, m, H2), 4.96 (1H, s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8 (C18), 19.9 (C11), 21.1 ($-CO\underline{C}H_3$), 31.7 (C12), 36.3 (C20), 38.9 (C13), 41.8 (C14), 42.8 (C1), 43.5 (C15), 45.4 (C3), 49.5 (C10), 51.4 (C6), 51.7 (C4 and $-CO_2\underline{C}H_3$ overlapped), 52.7 (C8), 54.1 (C9), 58.6 (C5), 68.3 (C2), 107.0 (C17), 157.1 (C16), 170.2 ($-\underline{C}OCH_3$), 173.4 (C7), 217.8 (C19).

MS (EI) *m/z* 386 (M^+, 1%), 355 (25), 326 (100), 295 (98), 284 (100), 266 (50), 239 (12), 225 (37), 183 (14), 155 (12), 129 (12), 105 (19), 79 (11). **HRMS** (EI) *m/z* calcd for M^+, $C_{23}H_{30}O_5$: 386.2093; found 386.2092.

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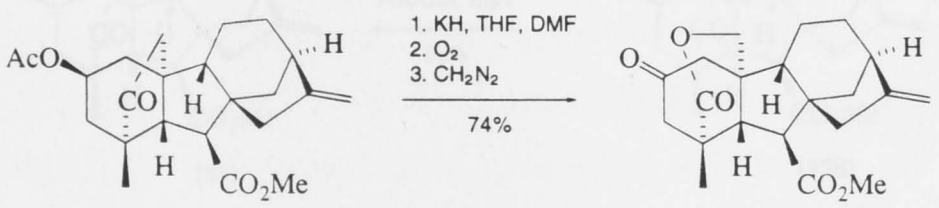
ent-2-oxo-20-hydroxy-gibberell-16-en-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (125)



(124) (125)

An excess of dry (oil free) potassium hydride (approximately 64 mg, 1.6 mmol) was added to a solution of the cyclopentanone **124** (32 mg, 0.083 mmol) in dry THF (5 ml) and dry DMF (5 ml) at 0°C with stirring under an atmosphere of nitrogen. The

reaction mixture was left stirring for 2 h, after which time the reaction flask was thoroughly flushed with nitrogen before a steady stream of dry oxygen gas was passed through the solution. After 20 min, TLC analysis indicated that the reaction had gone to completion. The reaction was throughly flushed with nitrogen then carefully quenched with methanol and the solvent removed *in vacuo*. The DMF was removed under high vacuum with gentle heating. The solid residue was dissolved in water (20 ml) and ethyl acetate (50 ml), the layers were separated and the aqueous phase was extracted with ethyl acetate (2x20 ml). The combined organic phases were washed with brine (10 ml), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. The residue was dissolved in methanol (10 ml) and treated with an excess of diazomethane. The solvent was removed under a gentle stream of nitrogen. Purification on silica gel (hexane/ethyl acetate, 3:1) afforded compound **125** (22 mg, 74%) as a colourless oil.

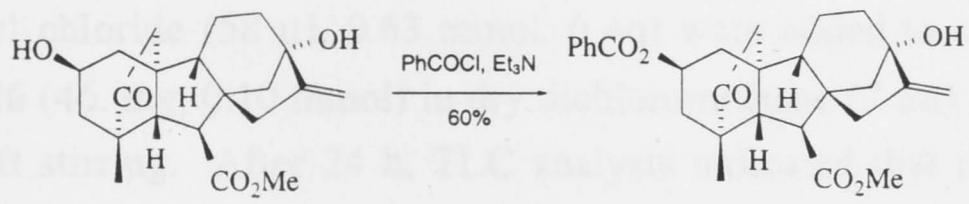
R_f : 0.83 (hexane:ethyl acetate, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (3H, s, H18), 0.80 - 2.30 (9H, m), 2.39 (1H, d, J = 15.4 Hz, H3), 2.49 (2H, s, H1), 2.66 (1H, m, H13), 2.74 (1H, d, J = 15.4 Hz, H3), 2.80 (1H, d, J = 12.6 Hz, H5), 2.85 (1H, d, J = 12.6 Hz, H6), 3.72 (3H, s, $-CO_2CH_3$), 4.11 (1H, d, J = 12.1 Hz, H20), 4.38 (1H, d, J = 12.1 Hz, H20), 4.83 (1H, br s, H17), 4.95 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 15.8 (C11), 22.3 (C18), 31.1 (C12), 36.3 (C14), 39.1 (C13), 43.5 (C15), 44.6 (C1), 46.2 (C4), 50.7 (C3), 51.1 (C6), 52.1 (C5), 52.2 ($-CO_2\underline{C}H_3$), 52.7 (C8), 53.3 (C10), 55.1 (C9), 74.2 (C20), 107.3 (C17), 155.8 (C16), 173.0, 173.8 (C7, C19), 205.0 (C2).

MS (EI) *m/z* 358 (M^+, 70%), 326 (37), 298 (66), 253 (100), 211 (22), 143 (23), 129 (28), 121 (23), 105 (28), 91 (49), 77 (27), 69 (33), 55 (34). **HRMS** (EI) *m/z* calcd for M^+, $C_{21}H_{26}O_5$: 358.1780; found 358.1780.

Methyl *ent*-2α-benzoyl-13-hydroxy-19-oxo-19,20-cyclogibberell-16-en-7-oate (126)



(**91**) (**126**)

Dry triethylamine (0.26 ml, 1.76 mmol, 10 eq) followed by benzoyl chloride (0.205 ml, 1.75 mmol, 10 eq) was added to a solution of the diol **91** (64 mg, 0.18 mmol) in dry dichloromethane (10 ml), and the reaction mixture was left stirring. After 24 h, TLC analysis indicated that the reaction was complete. Sat. sodium

bicarbonate was added to quench the reaction. After stirring for 10 min, the reaction mixture was diluted with ethyl acetate (50 ml), the layers were separated and the aqueous phase was extracted with ethyl acetate (2x10 ml). The combined organic phases were washed with brine (10 ml), dried over sodium sulfate and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 1:1) afforded the desired mono benzoate **126** (48.8 mg, 60% crude) as a colourless oil.

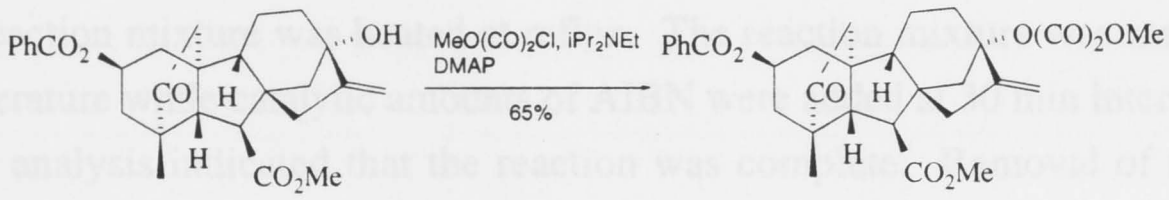
R_f : 0.52 (hexane:ethyl acetate, 1:1). **IR** 1735, 1715 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (3H, s, H18), 1.20 - 2.50 (16H, m), 2.43 (1H, d, J = 11.7 Hz, H5), 2.62 (1H, d, J = 11.7 Hz, H6), 3.71 (3H, s, -CO_2CH_3), 4.94 (1H, br s, H17), 5.15 (1H, 7-line multiplet, H2), 5.25 (1H, br s, H'17), 7.40 - 8.00 (5H, m, C_6H_5CO-).

^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8 (C18), 19.8 (C11), 38.5 (C12), 41.8 (CH_2), 42.7 (CH_2), 43.3 (CH_2), 44.0 (CH_2), 44.3 (CH_2), 49.2, 49.5 (C10, C4), 51.1 (C6), 51.9 (-$CO_2\underline{C}H_3$), 52.9 (C8), 53.8 (C9), 59.0 (C5), 68.8 (C2), 78.2 (C13), 106.9 (C17), 128.3, 129.4, 129.9, 133.0 ($\underline{C}_6H_5CO$-), 157.6 (C16), 165.6 ($C_6H_5\underline{C}O$-), 173.8 (C7), 217.4 (C19).

MS (EI) *m/z* 464 (M^+, 4%), 433 (15), 356 (12), 342 (100), 310 (64), 282 (41), 241 (29), 135 (29), 105 (86), 77 (48), 55 (20). **HRMS** (EI) *m/z* calcd for M^+, $C_{28}H_{32}O_6$: 464.2199; found 464.2198.

Methyl *ent*-2α-benzoyl-13-methyloxalyloxy-19-oxo-19,20-cyclogibberell-16-en-7-oate (127)



(126) (127)

DIPEA (110 µl, 0.63 mmol, 6 eq), plus a catalytic amount of DMAP, followed by methyloxalyl chloride (58 µl, 0.63 mmol, 6 eq) were added to a solution of the monoacetate **126** (46. mg, 0.10 mmol) in dry dichloromethane (7 ml) and the reaction mixture was left stirring. After 24 h, TLC analysis indicated that the reaction was complete. The reaction mixture was diluted with ethyl acetate (50 ml) and washed with sat. sodium bicarbonate solution (15 ml) and brine (15 ml). The combined aqueous phases were back-extracted with ethyl acetate (2x10 ml). The combined organic phases were dried over sodium sulfate, and the solvent removed *in vacuo*. Two lots of chromatography on silica gel (hexane/ethyl acetate, 3:1) afforded compound **127** (38 mg, 65%), mixed with approximately 10% of some unknown impurity.

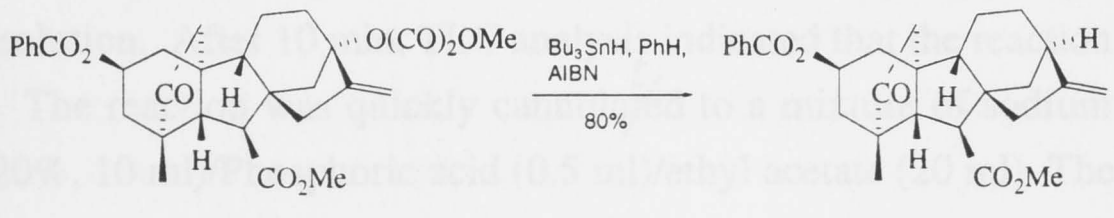
R_f : 0.93 (hexane:ethyl acetate, 1:2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (3H, s, H18), 1.20 - 2.50 (15H, m), 2.45 (1H, d, J = 11.9 Hz, H5), 2.64 (1H, d, J = 11.9 Hz, H6), 3.71 (3H, s, $-CO_2CH_3$), 3.89 (3H, s, $-(CO)_2-OCH_3$), 5.06 (1H, br s, H17), 5.15 (1H, 7-line multiplet, H2), 5.27 (1H, br s, H'17), 7.40 - 8.00 (5H, m, C_6H_5CO-).

^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8 (C18), 19.7 (C11), 36.2 (C20), 39.3 (C20), 41.8 (CH_2), 42.7 (CH_2), 43.2 (CH_2), 43.4 (CH_2), 49.2, 50.4 (C10, C4), 50.8 (C9), 52.0 ($-CO_2\underline{C}H_3$), 52.9 (C8), 53.4 (C6 and $-(CO)_2-O\underline{C}H_3$ overlapped), 58.9 (C5), 68.7 (C2), 87.5 (C13), 109.1 (C17), 128.3, 129.5, 129.9, 133.0 ($\underline{C}_6H_6CO-$), 152.1 (C16), 156.3, 158.2 ($-(\underline{C}O)_2-CH_3$), 165.6 ($C_6H_6\underline{C}O-$), 172.7 (C7), 216.9 (C19).

MS (EI) *m/z* 550 (M^+, 1%), 519 (7), 428 (58), 396 (62), 386 (52), 324 (84), 292 (28), 282 (38), 265 (24), 223 (30), 105 (100), 91 (22), 77 (34), 59 (20). **HRMS** (EI) *m/z* calcd for M^+-OCH_3, $C_{30}H_{31}O_8$: 519.2019; found 519.2020.

Methyl *ent*-2α-benzoyl-19-oxo-19,20-cyclogibberell-16-en-7-oate (128)



(127) (128)

Methyloxalyl ester **127** (38 mg, 0.07 mmol) was dissolved in dry toluene (5 ml) under a nitrogen atmosphere. Tributyltin hydride (38 µl, 0.14 mmol, 2 eq) was added and the reaction mixture was heated at reflux. The reaction mixture was maintained at this temperature while catalytic amounts of AIBN were added at 30 min intervals. After 1 h, TLC analysis indicated that the reaction was complete. Removal of the solvent *in vacuo*, followed by chromatography on silica gel (hexane/ethyl acetate, 5:1) afforded compound **128** (25.0 mg, 80%) as a colourless oil.

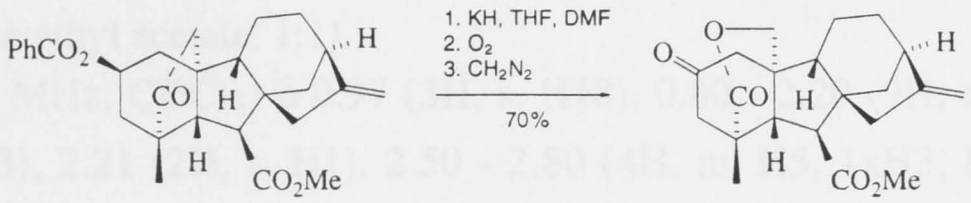
R_f : 0.96 (hexane:ethyl acetate, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (3H, s, H18), 1.10 - 2.60 (15H, m), 2.42 (1H, d, J = 11.9 Hz, H5), 2.59 (1H, d, J = 11.9 Hz, H6), 2.62 (1H, m, H13), 3.69 (3H, s, $-CO_2CH_3$), 4.84 (1H, br s, H17), 4.96 (1H, br s, H'17), 5.15 (1H, 7-line multiplet, H2), 7.30 - 8.00 (5H, m, C_6H_6CO-).

^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9 (C18), 19.0 (C11), 31.7 (C12), 36.3 (C20), 38.9 (C13), 41.9 (CH_2), 42.8 (CH_2), 43.5 (CH_2), 45.4 (C3), 49.5 (C10), 51.5 (C6), 51.7 ($-CO_2CH_3$), 51.8 (C4), 52.8 (C8), 54.1 (C9), 58.6 (C5), 68.9 (C2), 107.0 (C17), 128.3, 129.5, 130.0, 133.0 ($\underline{C}_6H_5CO-$), 157.1 (C16), 165.7 ($C_6H_6\underline{C}O-$), 173.4 (C7), 217.8 (C19).

MS (EI) *m/z* 448 (M^+, 1%), 417 (7), 326 (74), 294 (88), 284 (100), 266 (66), 225 (42), 183 (16), 155 (14), 105 (100), 91 (18), 77 (44). **HRMS** (EI) *m/z* calcd for M^+-OCH_3, $C_{27}H_{29}O_4$: 417.2066; found 417.2067.

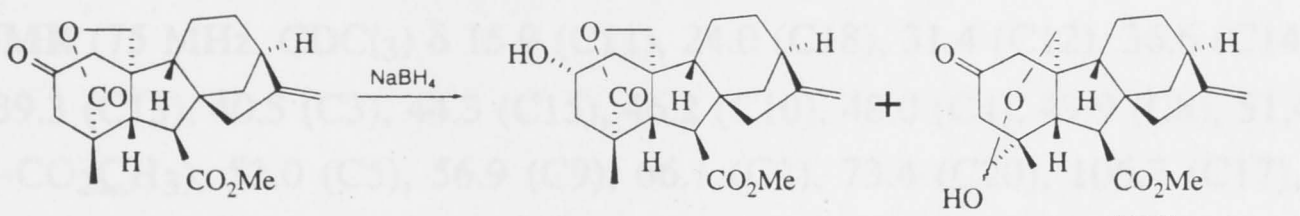
Oxidative Opening of the Protected Cyclopentanone (128)



(**128**) (**125**)

An excess of dry (oil free) potassium hydride (approximately 40 mg, 1.0 mmol) was added to a solution of the cyclopentanone **128** (25 mg, 0.055 mmol) in dry THF (2 ml) and dry DMF (2 ml) at 0°C with stirring under an atmosphere of nitrogen. The reaction mixture was left stirring for 1.5 h, after which time the reaction flask was thoroughly flushed with nitrogen before a steady stream of dry oxygen gas was passed through the solution. After 10 min, TLC analysis indicated that the reaction had gone to completion. The reaction was quickly cannulared to a mixture of sodium dihydrogen phosphate (20%, 10 ml)/Phosphoric acid (0.5 ml)/ethyl acetate (20 ml). The layers were separated and the organic phase was washed to pH =4 with brine (4x10 ml). The combined aqueous phase was back extracted with ethyl acetate (3x 10 ml). The organic extractions were washed with brine (10 ml), the combined organic phases were dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Purification on silica gel (hexane/ethyl acetate, 3:1) afforded compound **125** (14 mg, 70%) as a colourless oil.

Reduction of 2-oxo-GA_{15} (125)



(**125**) (**129**) (**130**)
3:1 mixture of isomers

Sodium borohydride (1.3 mg, 0.03 mmol) was added to a solution of the keto-lactone **125** (12 mg, 0.03 mmol) in methanol (3 ml) at 0°C. After 15 min TLC analysis showed that the reaction was complete. The solution was diluted with ethyl actetate (30 ml) and acidified with sodium dihydrogen phosphate solution (20%, 5 ml). The layers were separated and the aqueous phase was extracted with ethyl acetate (2x10 ml).

The combined organic phases were washed with brine (2x5 ml), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 2:1) afforded in order of elution:

Methyl *ent*-2-oxo-20,19,19-trihydroxy-gibberell-16-en-7-oate (**130**, 4.3 mg, 36%, 2 isomers, approx. 3:1 ratio, only major isomer assigned below)

R_f : 0.53 (hexane:ethyl acetate, 1:1).
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (3H, s, H18), 0.80 - 2.20 (9H, m), 2.17 (1H, d, J = 15.7 Hz, H3), 2.21 (2H, s, H1), 2.50 - 2.80 (4H, m, H5, 1xH3, H13), 3.68 (1H, d, J = 11.6 Hz, H6), 3.67 (1H, d, J = 11.4 Hz, H20), 3.73 (3H, s, $-CO_2CH_3$), 4.06 (1H, d, J = 11.5 Hz, H20), 4.74 (1H, d, J = 4.4 Hz, H19), 4.82 (1H, br s, H17), 4.94 (1H, br s, H'17).
^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9 (C11), 22.5 (C18), 31.9 (C12), 36.2 (C14), 38.8 (C4), 39.2 (C13), 45.6 (C15), 46.0 (C1), 50.2 (C6), 50.7 (C3), 51.9 (C5), 52.9 ($-CO_2\underline{C}H_3$), 53.3 (C8), 53.7 (C10), 54.8 (C9), 62.3 (C20), 98.7 (C19), 106.8 (C17), 157.1 (C16), 174.8 (C7), 208.0 (C2).
MS (EI) *m/z* 360 (M^+, 18%), 342 (100), 310 (35), 284 (82), 239 (52), 223 (89), 171 (48), 143 (48), 129 (58), 105 (67), 91 (82), 71 (65), 55 (63). **HRMS** (EI) *m/z* calcd for M^+, $C_{21}H_{28}O_5$: 360.1937; found 360.1936.

***ent*-2α,20-Dihydroxy-gibberell-16-en-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone** (**129**, 3.7 mg, 31%)

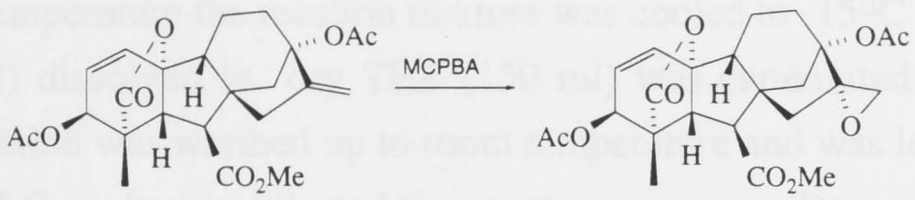
R_f : 0.16 (hexane:ethyl acetate, 1:1). **IR** 1730 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (3H, s, H18), 0.80 - 2.30 (14H, m), 2.11 (1H, d, J = 12.6 Hz, H5), 2.65 (1H, m, H13), 2.84 (1H, d, J = 12.6 Hz, H6), 3.68 (3H, s, $-CO_2CH_3$), 4.24 (1h, br s, H2), 4.33 (1H, d, J = 11.3 Hz, H20), 4.37 (1H, d, J = 11.3 Hz, H20), 4.81 (1H, br s, H17), 4.94 (1H, br s, H'17).
^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9 (C11), 24.0 (C18), 31.4 (C12), 36.6 (C14), 39.2 (C1), 39.3 (C13), 40.5 (C3), 44.3 (C15), 46.2 (C10), 48.0 (C4), 49.9 (C8), 51.4 (C6), 51.8 ($-CO_2\underline{C}H_3$), 52.0 (C5), 56.9 (C9), 66.1 (C2), 73.4 (C20), 106.7 (C17), 156.6 (C16), 173.7, 176.2 (C7, C19).
MS (EI) *m/z* 360 (M^+, 65%), 329 (27), 310 (60), 282 (79), 255 (46), 237 (82), 195 (45), 143 (43), 129 (65), 91 (72), 73 (80), 57 (100). **HRMS** (EI) *m/z* calcd for M^+, $C_{21}H_{28}O_5$: 360.1937; found 360.1936.##

The procedure above is a representation only as zinc borohydride, as well as sodium borohydride at three different temperatures (-78°C, 0°C and room temperature). Each reaction gave the same products in similar ^{1}H NMR yields.

8.5 Chapter 5 Experimental

8.5.1 Introduction

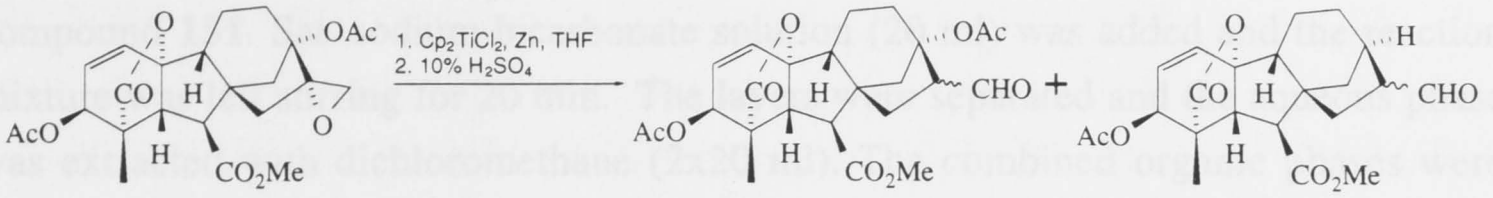
ent-3α,13-Diacetoxy-10β-hydroxy-16β,17-epoxy-20-norgibberell-1-en-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (33)



(**32**) (**33**)

The water was removed from a solution of m-chloroperbenzoic acid (28 g, 60% stabilized with water, 0.1 mol) in dichloromethane (350 ml) by pasteur pipette, followed by drying over sodium sulfate. The dichloromethane solution was then added to a solution of compound **32** (35 g, 0.0788 mol) in dry dichloromethane (500 ml) with stirring under a nitrogen atmosphere at -15°C. The solution was then allowed to warm slowly to 4°C and was kept at this temperature. After 4 days, TLC analysis indicated that the reaction was complete. Saturated sodium bicarbonate solution (150 ml) was added and the reaction left to stir for 1.5 h. The layers were separated and the aqueous phase was extracted with dichloromethane (2x50 ml). The combined organic phases were dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. The oily residue was passed through a short plug of silica gel (dichloromethane). The solvent was removed and the residue was recrystallized (petrolium spirit/ethyl acetate, 2:1, 180 ml), to yield the desired α-epoxide **33** (29.1 g, 80%, identical with an authentic sample). The mother liquors were reduced and provided a 1:1 mixture of the α and β epoxides mixed with a small amount of benzoic acid impurity (5g, 14%).

Opening of the Epoxide: Deacetylation.

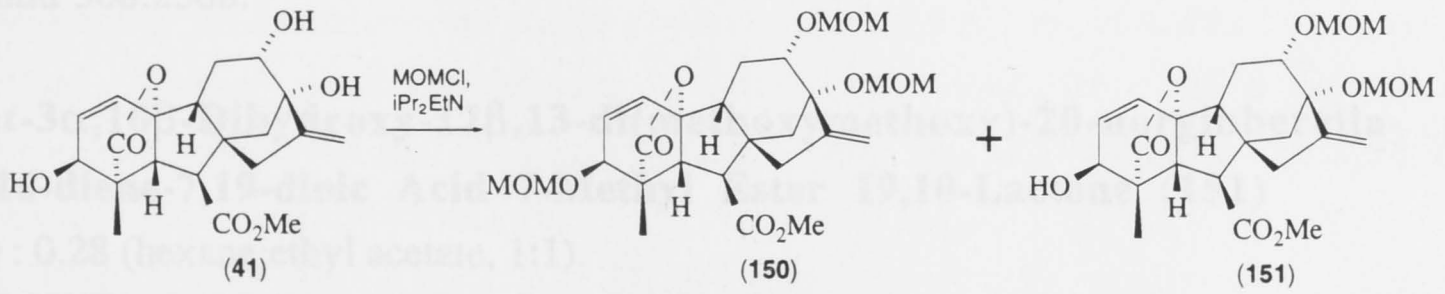


(**33**) (**148**) (**149**)

Zinc powder (4.2 g, 0.064 mol) was added to a solution of titanocene dichloride (15 g, 0.06 mol) in dry THF (400 ml) stirring under a nitrogen atmosphere. After 2 h of stirring at room temperature the reaction mixture was cooled to -15°C and compound **33** (6.1 g 0.013 mol) dissolved in dry THF (150 ml) was cannulated into the reaction mixture. The reaction was warmed up to room temperature and was left stirring for 1 h. After this time TLC analysis indicated the reaction was complete, so the reaction was cooled to 0°C and sulfuric acid (10%, 100 ml) was added. The reaction mixture was diluted with ether (500 ml) and the acid was neutralised with solid sodium bicarbonate. The layers were separated and the aqueous layer was extracted with ether (2x100 ml). The combined organic phases were washed with brine (2x200 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Purification of the residue on silical gel (hexane/ethyl acetate, 3:1 - 1:1) provided two compounds: the 13-deoxy compound **149** (2.3 g, 43%), followed by the expected compound **148** (0.8 g, 13%) (both compounds had NMR spectra identical to authetic compounds).

6.5.2 12α,13α-DIHYDROXY SERIES

***ent*-10β-Hydroxy-3α,12β,13-tri(methoxymethoxy)-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (150)**



(**41**) (**150**) (**151**)

DIPEA (2.60 ml, 15.0 mmol, 13 eq), a catalytic amount of DMAP, followed by chloromethyl methyl ether (1.00 ml 13.1 mmol, 12 eq) were added to a solution of compound **41** ** (410 mg, 1.10 mmol) in dry dichloromethane (30 ml) at 0°C under an

** Prepared following the procedure of Chu[32,33] and Bhaskar [34]

atmosphere of nitrogen, and the reaction left to warm to room temperature. After 4 days, TLC analysis indicated a mixture of the desired product **150**, plus the mono-hydroxy compound **151**. Sat. sodium bicarbonate solution (20 ml) was added and the reaction mixture was left stirring for 20 min. The layers were separated and the aqueous phase was extracted with dichloromethane (2x20 ml). The combined organic phases were washed with hydrochloric acid (1M, 2x20 ml), then with brine (2x20ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatograhy on silica gel (hexane/ethyl acetate, 2:1 - 1:1) afforded compound **150** (387 mg, 70%) as a colourless oil followed by the mono-hydroxy compound **151** (113 mg, 20%).

***ent*-10β-Hydroxy-3α,12β,13-tri(methoxymethoxy)-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (150)**

R_f : 0.68 (hexane:ethyl acetate, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (3H, s, H18), 1.70 - 2.20 (7H, m), 2.77 (1H, d, J = 10.5 Hz, H6), 3.26 (1H, d, J = 10.5 Hz, H5), 3.33, 3.36, (3x3H, s, -$OCH_2OC\underline{H}_3$), 3.67 (1H, t, J = 7.9 Hz, H12), 3.73 (3H, s, -CO_2CH_3), 3.99 (1H, d, J = 3.5 Hz, H3), 4.59, 4.72 (2x1H, ABd, J = 7.0 Hz, 3-$OC\underline{H}_2OCH_3$†), 4.65, 4.90 (2x1H, ABd, J = 6.8 Hz, 13-$OC\underline{H}_2OCH_3$†), 4.66, 4.72 (2x1H, d, J = 6.9 Hz, 12 $OC\underline{H}_2OCH_3$†), 5.17 (1H, br s, H17), 5.21 (1H, br s, H'17), 5.93 (1H, dd, J_1 = 9.4 Hz, J_2 = 3.5 Hz, H2), 6.27 (1H, d, J = 9.4, Hz, H1).

^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3 (C18), 25.9 (C11), 37.1 (C14), 43.8 (C15), 47.2 (C9), 50.1 (C6), 50.6 (C8), 51.9 (-$CO_2\underline{C}H_3$), 53.1 (C5), 53.3 (C4), 55.0, 55.1 and 55.5 (12-$OCH_2O\underline{C}H_3$, 3-$OCH_2O\underline{C}H_3$, 13-$OCH_2O\underline{C}H_3$), 74.8 (C3), 79.6 (C12), 84.7 (C13), 89.9 (13-$O\underline{C}H_2OCH_3$), 91.8 (C10), 96.6, 96.9 (12-$O\underline{C}H_2OCH_3$, 3 $O\underline{C}H_2OCH_3$), 111.3 (C17), 131.2 (C1), 132.0 (C2), 150.8 (C16), 172.2 (C7), 177.8 (C19).

MS (EI) *m/z* 508 (M^+, 4%), 477 (10), 463 (13), 446 (18), 420 (20), 401 (20), 385 (31), 371 (20), 357 (34), 341 (60), 325 (60), 309 (76), 281 (100), 267 (74), 249 (38), 235 (32), 223 (34), 209 (48). **HRMS** (EI) *m/z* calcd for M^+, $C_{26}H_{36}O_{10}$: 508.2308; found 508.2308.

***ent*-3α,10β-Dihydroxy-12β,13-di(methoxymethoxy)-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (151)**

R_f : 0.28 (hexane:ethyl acetate, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (3H, s, H18), 1.70 - 2.30 (8H, m), 2.80 (1H, d, J = 11.0 Hz, H6), 3.17 (1H, d, J = 11.0 Hz, H5), 3.34, 3.37 (2x3H, s, 13-$OCH_2OC\underline{H}_3$, 12-$OCH_2OC\underline{H}_3$), 3.68 (1H, t, J = 6.6 Hz, H12), 3.74 (3H, s, -CO_2CH_3), 4.16 (1H, d, J = 3.7 Hz, H3), 4.60, 4.73 (2x1H, ABd, J = 7.0 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.66, 4.91 (2x1H, ABd, J = 6.8 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.18 (1H,

br s, H17), 5.23 (1H, br s, H'17), 5.90 (1H, dd, J_1 = 9.3 Hz, J_2 = 3.7 Hz, H2), 6.31 (1H, d, J = 9.3 Hz, H1).

^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (C18), 26.0 (C11), 37.2 (C14), 43.9 (C15), 47.3 (C9), 50.1 (C6), 50.8 (C8), 52.2 (-$CO_2\underline{C}H_3$), 52.8 (C5), 53.4 (C4), 55.2 (12-$OCH_2O\underline{C}H_3$ and 13-$OCH_2O\underline{C}H_3$ overlapped), 69.5 (C3), 79.7 (C12), 84.8 (C13), 90.1 (13-$O\underline{C}H_2OCH_3$), 91.9 (C10), 97.0 (12-$O\underline{C}H_2OCH_3$), 111.6 (C17), 132.2 (C1), 132.6 (C2), 150.8 (C16), 172.6 (C7), 178.4 (C19).

MS (EI) *m/z* 464 (M^+, 2%), 433 (4), 419 (40), 387 (20), 357 (26), 325 (37), 281 (46), 267 (71), 253 (50), 237 (43), 223 (60), 209 (100), 181 (40), 91 (62). **HRMS** (EI) *m/z* calcd for M^+, $C_{24}H_{32}O_9$: 464.2046; found 4664.2048.

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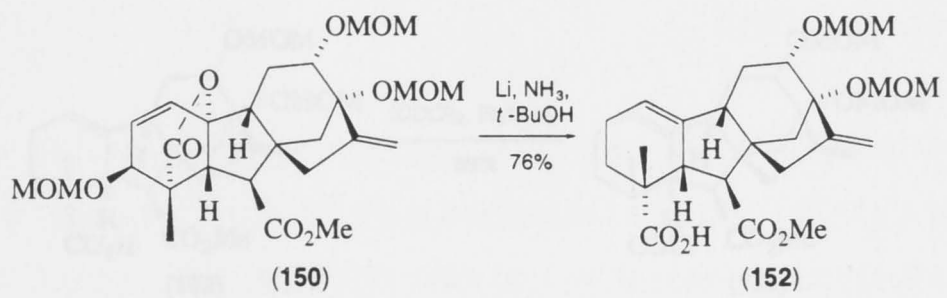
ent-12β,13-Di(methoxymethoxy)-20-norgibberella-1(10),16-diene-7,19-dioic Acid 7-Methyl Ester (152)



(150) (152)

Compound **150** (215 mg, 0.42 mmol) was dissolved in dry THF (2 ml) containing *t*-butyl alcohol (300 µl, 3.2 mmol, 7.5 eq). After cooling to -78°C, liquid ammonia (approximately 20 ml) was distilled into the flask from a sodium amide solution. Lithium metal (approximately 14 mg, 2.0 mg atom) was added in small pieces with vigorous stirring. The reaction was quenched with saturated ammonium chloride solution (5 ml) upon appearance of a persistent deep blue colour; the ammonia was allowed to evaporate under a gentle flow of nitrogen. The white solid residue was dissolved in phosphoric acid (10%, 20 ml) and ethyl acetate (50 ml), the layers were separated and the aqueous layer was extracted with ethyl acetate (2x10 ml). The combined organic phases were washed with brine (3x15 ml) to pH 4, dried over sodium sulfate, filtered, and the solvent removed *in vacuo* to yield a yellow oil. Chromatography (hexane/ethyl acetate/acetic acid, 2:1:0.1) afforded the acid **152** (145 mg, 76%) as a colourless oil.

R_f : 0.20 (hexane:ethyl acetate, 1:1). **IR** 1720 cm^{-1}.

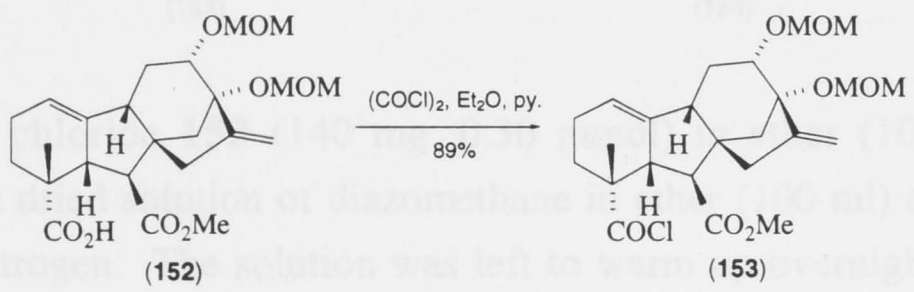
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (3H, s, H18), 1.28 - 2.60 (12H, m), 2.84 (1H, br s, H5), 3.15 (1H, d, J = 5.8 Hz, H6), 3.31, 3.41 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.54 (1H, d, J = 5.3 Hz, H12), 3.70 (3H, s, -CO_2CH_3), 4.54, 4.72 (2x1H, ABd,

J = 6.9 Hz, 12-OC<u>H</u>$_2$OCH$_3$†), 4.69, 4.81 (2x1H, ABd, J = 6.5 Hz, 13-OC<u>H</u>$_2$OCH$_3$†), 5.04 (1H, br s, H17), 5.06 (1H, br s, H'17), 5.48 (1H, br s, H1)

^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1 (C2), 24.7 (C11), 26.1 (C18), 34.4 (C3), 37.4 (C14), 38.8 (C15), 43.3 (C8), 45.9 (C9), 49.7 (C4), 50.0, 50.8 (C6, C5), 51.5 -CO_2<u>C</u>H$_3$), 54.7, 55.2 (12-OCH$_2$O<u>C</u>H$_3$, 13-OCH$_2$O<u>C</u>H$_3$), 79.2 (C12), 87.2 (C13), 91.3 (13-O<u>C</u>H$_2$OCH$_3$), 96.3 (12-O<u>C</u>H$_2$OCH$_3$), 108.0 (C17), 114.6 (C1), 140.9 (C10), 150.0 (C16), 176.6 (C7), 181.0 (C19).

MS (EI) *m/z* 450 (M^+, 20%), 405 (43), 388 (20), 373 (33), 343 (38), 328 (53), 314 (47), 297 (51), 283 (100), 255 (39), 239 (42), 211 (49), 101 (66), 58 (100). **HRMS** (EI) *m/z* calcd for M^+, $C_{24}H_{34}O_8$: 450.2254; found 450.2253.

Methyl *ent*-19-chloro-12β,13-di(methoxymethoxy)-19-oxo-20-norgibberella-1(10),16-dien-7-oate (153)



A vigorously stirred solution of oxalyl chloride (0.28 ml, 3.2 mmol, 10eq) in dry ether (10 ml) containing DMF (1 µl) under an atmosphere of nitrogen was cooled to -30°C. To this solution was slowly added the acid **152** (145 mg, 0.32 mmol) dissolved in dry ether (2.5 ml) and pyridine (0.8 ml). The solution was then left overnight to warm up to room temperature. The reaction was worked up by filtering through a sintered funnel and washing the solid residue throughly with dry ether (5x20 ml). The solvent was removed *in vacuo* and excessive oxalyl chloride and pyridine were removed by azeotroping with dry benzene (4x30 ml). Finally, filtration through a small plug of Celite followed by removal of the solvent *in vacuo* furnished the desired acid chloride **153** (134 mg, 89%) as a yellow oil.

IR 1814, 1725 cm^{-1}.

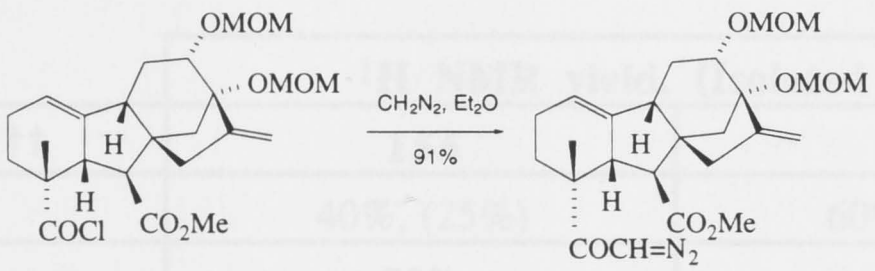
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (3H, s, H18), 1.70 - 2.60 (11H, m), 2.93 (1H, d, J = 6.4 Hz, H6), 2.96 (1H, br s, H5), 3.34, 3.40 (2x3H, s, -OCH$_2$OC<u>H</u>$_3$), 3.56 (1H, d, J = 5.2 Hz, H12), 3.70 (3H, s, -CO_2CH_3), 4.57, 4.74 (2x1H, ABd, J = 6.9 Hz, 12-OC<u>H</u>$_2$OCH$_3$†), 4.69, 4.82 (2x1H, ABd, J = 6.5 Hz, 13-OC<u>H</u>$_2$OCH$_3$†), 5.05 (1H, br s, H17), 5.08 (1H, br s, H'17), 5.45 (1H, br s, H1).

^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7 (C2), 24.7 (C11), 25.3 (C18), 35.8 (C14), 37.7 (C3), 39.2 (C15), 45.9 (C9), 50.0 (C6), 50.1 (C8), 51.1 (C5), 51.7 (-CO_2<u>C</u>H$_3$), 54.1

(C4), 55.2, 55.3 (13-$OCH_2O\underline{C}H_3$, 12-$OCH_2O\underline{C}H_3$), 79.1 (C12), 87.2 (C13), 91.6 (13-$O\underline{C}H_2OCH_3$), 96.3 (12-$O\underline{C}H_2OCH_3$), 108.2 (C17), 113.8 (C1), 140.9 (C10), 149.8 (C16), 175.7, 176.2 (C7, C19).

MS (EI) *m/z* 468 (M^+, 6%), 423 (17), 344 (16), 328 (47), 299 (29), 283 (100), 269 (24), 255 (35), 239 (53), 211 (36), 197 (17). **HRMS** (EI) *m/z* calcd for M^+, $C_{24}H_{33}O_7{}^{35}Cl$: 468.1915; found 468.1914.

Methyl *ent*-12β,13-di(methoxymethoxy)-19-diazomethyl-19-oxo-20-norgibberella-1(10),16-dien-7-oate (154)



(153) (154)

The acid chloride **153** (140 mg, 0.30 mmol) in ether (10 ml) was slowly cannulated into a dried solution of diazomethane in ether (100 ml) at -30°C under an atmosphere of nitrogen. The solution was left to warm up overnight, whereupon the reaction was judged to be complete by TLC analysis. The solvent was removed *in vacuo* and the residue was purified on silica gel (hexane/ethyl acetate, 2:1) to yield the diazoketone **154** (130 mg, 91%) as a yellow oil.

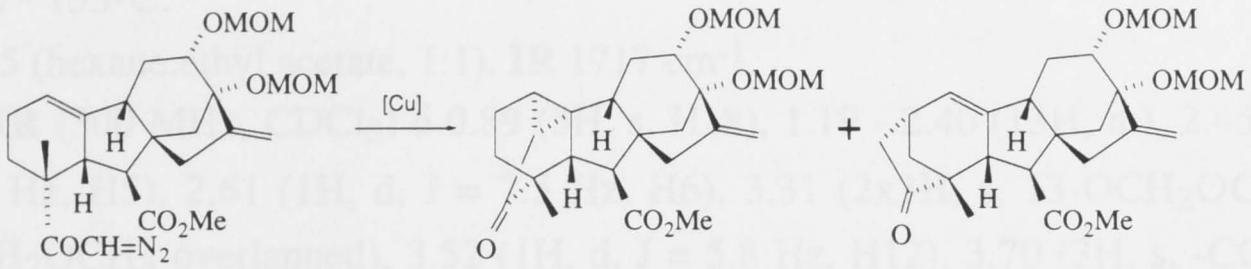
R_f : 0.65 (hexane:ethyl acetate, 1:1). **IR** 2107, 1727, 1639 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (3H, s, H18), 1.60 - 2.60 (11H, m), 2.80 (1H, br s, H5), 2.90 (1H, d, J = 6.4 Hz, H6), 3.32, 3.41 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.56 (1H, d, J = 5.3 Hz, H12), 3.68 (3H, s, -CO_2CH_3), 4.55, 4.72 (2x1H, ABd, J = 6.9 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.70, 4.82 (2x1H, ABd, J = 6.5 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.04 (1H, br s, H17), 5.07 (1H, br s, H'17), 5.43 (1H, s, -$COCH=N_2$), 5.47 (1H, br s, H1).

^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0 (C2), 24.8 (C11), 26.1 (C18), 33.9 (C3), 37.6 (C14), 39.2 (C15), 42.0 (C9), 46.5 (C8), 49.7 (C4), 50.2, 51.1 (C6, C5), 51.5 (-$CO_2\underline{C}H_3$), 53.7 (19-$CO\underline{C}H=N_2$), 55.1, 55.3 (13-$OCH_2O\underline{C}H_3$, 12-$OCH_2O\underline{C}H_3$), 79.1 (C12), 87.1 (C13), 91.5 (13-$O\underline{C}H_2OCH_3$), 96.3 (12-$O\underline{C}H_2OCH_3$), 108.1 (C17), 114.2 (C1), 141.6 (C10), 150.1 (C16), 176.5 (C7), 197.2 (C19).

MS (EI) *m/z* 446 (M^+-N_2, 13%), 430 (8), 415 (19), 401 (100), 369 (82), 339 (60), 311 (48), 281 (51), 251 (56), 237 (68), 211 (52), 195 (39), 179 (34) 143 (34), 121 (38), 105 (49), 91 (51). **HRMS** (EI) *m/z* calcd for M^+-N_2, $C_{25}H_{34}O_7$: 446.2305; found 446.2305.

Methyl *ent*-12β,13-di(methoxymethoxy)-19-oxo-1β,20-cyclo-19,20-cyclogibberell -16-en-7-oate (155)



(154) (155) (156)

Table 7: Results from Cyclopropanation Reactions

	^{1}H NMR yield, (Isolated yield)	
Procedure ††	**155**	**156**
A‡‡ (copper-bronze)	40%, (25%)	60%, (44%)
B (copper(II)acetylacetonate)	75%	25%
C (di-*t*-butylsalicyl-imidato cuprate)	40%	60%

††General proceedures from p 98

‡‡Purification of the reaction mixture on silica gel (hexane/ethyl acetate, 3:1) provided in order of elution.

Methyl *ent*-12β,13-di(methoxymethoxy)-19-oxo-2,19-methanogibberella-1(10),16-dien-7-oate (**156**, oil).

R_f : 0.75 (hexane:ethyl acetate, 1:1). **IR** 1732 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (3H, s, H18), 1.20 - 2.40 (11H, m), 2.56 (1H, d, J = 6.6 Hz, H6), 2.81 (1H, br s, H5), 3.10 (1H, m, H2), 3.30, 3.40 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.52 (1H, m, H12), 3.69 (3H, s, -CO_2CH_3), 4.52, 4.65 (2x1H, ABd, J = 6.7 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.65, 4.82 (2x1H, ABd, J = 6.5 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.00 (2H, apparent br t, J = 2.7 Hz, H17), 5.84 (1H, m, H1).

^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2 (C18), 25.9 (C11), 31.0 (C2), 37.3 (19-$CO\underline{C}H_2$-), 39.0 (C15†), 44.2 (C14†), 45.1 (C9), 49.2 (C6), 49.3 (C3), 49.8, 50.4 (C8, C4), 51.6 (-$CO_2\underline{C}H_3$), 54.5 (C5), 55.3 (13-$OCH_2O\underline{C}H_3$ and 12-$OCH_2O\underline{C}H_3$ overlapped), 78.9 (C12), 86.9 (C13), 91.4 (13-$O\underline{C}H_2OCH_3$), 96.5 (12-$O\underline{C}H_2OCH_3$), 108.4 (C17), 122.5 (C1), 141.0 (C10), 149.4 (C16), 175.8 (C7), 219.7 (C19).

MS (EI) *m/z* 446 (M^+, 14%), 415 (9), 401 (100), 369 (62), 339 (51), 310 (35), 283 (28), 267 (32), 251 (37), 237 (39), 211 (33), 195 (29), 181 (23), 143 (28), 119 (42), 105 (47), 69 (32). **HRMS** (EI) *m/z* calcd for M^+, $C_{25}H_{34}O_7$: 446.2305; found 446.2305.

Methyl *ent*-12β,13-di(methoxymethoxy)-19-oxo-1β,20-cyclo-19,20-cyclogibberell-16-en-7-oate (**155** white crystalline solid).

mp 150 - 153°C.

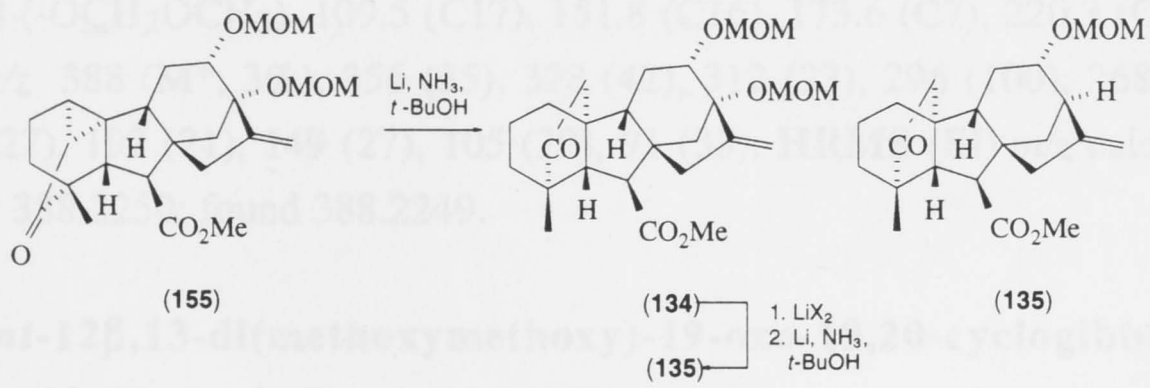
R_f : 0.65 (hexane:ethyl acetate, 1:1). **IR** 1717 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, s, H18), 1.19 - 2.40 (13H, m), 2.45 (1H, d, J = 7.5 Hz, H5), 2.61 (1H, d, J = 7.5 Hz, H6), 3.31 (2x3H, s, 13-$OCH_2OC\underline{H}_3$ and 12-$OCH_2OC\underline{H}_3$ overlapped), 3.52 (1H, d, J = 5.8 Hz, H12), 3.70 (3H, s, -CO_2CH_3), 4.50, 4.72 (2x1H, ABd, J = 7.2 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.60, 4.83 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.15 (2H, br s, H17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3 (C18), 17.3 (C2), 25.9 (C11), 29.2 (C1), 32.4 (-CO$\underline{C}$H-), 38.6, 38.7 (C3, C14), 41.2 (C10), 43.4 (C9), 44.8 (C15), 47.9 (C4), 51.1, 51.3 (C6, C5), 51.6 (C8), 51.7 (-$CO_2\underline{C}H_3$), 55.2, 55.3 (12-$OCH_2O\underline{C}H_3$, 13-$OCH_2O\underline{C}H_3$), 78.6 (C12), 86.2 (C13), 91.5 (13-$O\underline{C}H_2OCH_3$), 96.7 (12-$O\underline{C}H_2OCH_3$), 109.2 (C17), 149.6 (C16), 174.7 (C7), 214.7 (C19).

MS (EI) *m/z* 446 (M^+, 16%), 415 (14), 401 (100), 385 (10), 370 (40), 353 (14), 338 (30), 281 (26), 175 (38), 143 (26), 129 (26), 105 (38), 91 (40). **HRMS** (EI) *m/z* calcd for M^+, $C_{25}H_{34}O_7$: 446.2305; found 446.2305.

Methyl *ent*-12β,13-di(methoxymethoxy)-19-oxo-19,20-cyclogibberell-16-en-7-oate (**134**) and **Methyl-*ent*-12β–methoxymethoxy-19-oxo-19,20-cyclogibberell-16-en-7-oate** (**135**)



Compound **155** (52 mg, 0.12 mmol) was dissolved in dry THF (3.0 ml) together with *t*-butyl alcohol (35 µl, 0.37 mmol). After cooling to -78°C, liquid ammonia (approximately 15 ml) was distilled into the flask from a sodium amide solution. Lithium metal (approximately 3.5 mg, 0.72 mg atom) was added in small pieces with vigorous stirring. The reaction was quenched with saturated ammonium chloride solution (5 ml), upon the appearance of a deep blue colour that persisted for 5 sec. The ammonia was then allowed to evaporate under a gentle follow of nitrogen. The white solid residue was dissolved in water (10 ml) and ethyl acetate (50 ml), the layers were separated and the aqueous layer was extracted with ethyl acetate (2x10 ml). The combined organic phases

were washed with brine (15 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo* to yield a yellow oil. The residue was dissolved in dichloromethane (10 ml) and treated with Dess-Martin periodinane (100 mg, 0.24 mmol, 2 eq). After 15 min, when TLC analysis indicated that the reaction was complete, sat. sodium bicarbonate solution containing 7% sodium thiosulfate (20 ml) was added and the reaction mixture was left stirring until the cloudiness had dissipated. The reaction mixture was diluted with ethyl acetate (60 ml), the layers were separated and the organic phase was washed with sat. sodium bicarbonate solution (10 ml), brine (10 ml) and the combined aqueous phases were back-extracted with ethyl acetate (2x20 ml). The combined organic phases were dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 2:1) afforded the following two compounds, in order of elution.

Methyl *ent*-12β-methoxymethoxy-19-oxo-19,20-cyclogibberell-16-en-7-oate (**135**, 22.6 mg, 50%, slightly coloured oil).
R_f : 0.78 (hexane:ethyl acetate, 1:1). **IR** 1731 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, s, H18), 1.10 - 2.20 (15H, m), 2.35 (1H, d, J = 11.9 Hz, H5), 2.45 (1H, d, J = 11.9 Hz, H6), 2.71 (1H, d, J = 4.5 Hz, H13), 3.37 (3H, s, $-OCH_2OC\underline{H}_3$), 3.65 (1H, m, H12), 3.68 (3H, s, $-CO_2CH_3$), 4.64, 4.74 (2x1H, ABd, J = 6.7 Hz, $-OC\underline{H}_2OCH_3$), 5.00 (1H, br s, H17), 5.05 (1H, br s, H'17).
^{13}C NMR (75 MHz, $CDCl_3$) δ 17.1 (C18), 19.8 (C2), 27.9 (C11), 34.1 ($-CO\underline{C}H_2-$), 36.5 (C14), 38.1 (C3), 43.6 (C1), 45.6, 46.5 (C15, C13), 49.1 (C10), 50.7 (C9), 51.1 (C4), 51.7 ($-CO_2\underline{C}H_3$), 52.0 (C6), 53.6 (C8), 55.3 ($-OCH_2O\underline{C}H_3$), 59.4 (C5), 80.3 (C12), 94.8 ($-O\underline{C}H_2OCH_3$), 109.5 (C17), 151.8 (C16), 173.6 (C7), 220.3 (C19).
MS (EI) *m/z* 388 (M^+, 3%), 356 (35), 328 (42), 312 (23), 296 (100), 268 (32), 253 (20), 225 (27), 197 (21), 149 (27), 105 (29), 91 (33). **HRMS** (EI) *m/z* calcd for M^+, $C_{23}H_{32}O_5$: 388.2250; found 388.2249.

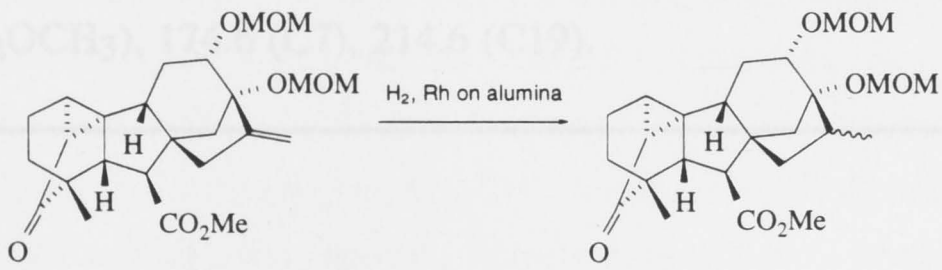
Methyl *ent*-12β,13-di(methoxymethoxy)-19-oxo-19,20-cyclogibberell-16-en-7-oate (**134**, 20 mg, 38%, colourless oil).
R_f : 0.62 (hexane:ethyl acetate, 1:1). **IR** 1731 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, s, H18), 1.20 - 2.20 (15H, m), 2.32 (1H, d, J = 11.9 Hz, H5), 2.44 (1H, d, J = 11.9 Hz, H6), 3.34, 3.36 (2x3H, s, $-OCH_2OC\underline{H}_3$), 3.89 (1H, t, J = 7.4 Hz, H12), 3.89 (3H, s, $-CO_2CH_3$), 4.58, 4.72 (2x1H, ABd, J = 6.9 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.68, 4.93 (2x1H, ABd, J = 6.7 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.18 (1H, br s, H17), 5.20 (1H, br s, H'17).
^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9 (C18), 19.7 (C2), 29.6 (C11), 36.5 ($-CO\underline{C}H_2-$), 37.2 (C14), 38.0 (C3), 43.4 (C1), 45.2 (C15), 49.2, 49.3 (C10, C4), 50.4, 51.7 (C9, C6), 51.8 ($-CO_2\underline{C}H_3$), 53.7 (C8), 55.2, 55.3 (13-$OCH_2O\underline{C}H_3$, 12-$OCH_2O\underline{C}H_3$), 59.6

(C5), 80.3 (C12), 85.2 (C13), 91.8 (13-O$\underline{C}H_2OCH_3$), 97.3 (12-O$\underline{C}H_2OCH_3$), 111.2 (C17), 151.4 (C16), 173.3 (C7), 219.9 (C19).
MS (EI) *m/z* 448 (M^+, 2%), 417 (14), 403 (100), 387 (34), 371 (65), 355 (39), 341 (36), 327 (40), 311 (22), 269 (18), 149 (40), 118 (36), 105 (53). **HRMS** (EI) *m/z* calcd for M^+, $C_{25}H_{36}O_7$: 448.2461; found 448.2460.

When the reaction above was repeated (cyclopentanone **155**, 60 mg, 0.133 mmol) and was quenched just as the blue/grey colour began to appear, the following product ratio was obtained, compound **134** (47 mg, 78%) and compound **135** (7 mg, 11%). If the reaction (cyclopentanone **155**, 205 mg, 0.23 mmol) was reduced so that the blue colour persisted for at least 30 sec (with approximately 6eq of lithium, 16.5 mg, 3.4 mg atom) , the following product ratio was obtained, compound **134** (89 mg, 50%) and compound **135** (50 mg, 25%), plus other reduction products resulting from the reduction of the 7-methyl ester function.

It was found if the reaction was repeated using the 13-methoxymethyl compound **134** (70 mg, 0.156 mmol) only a small amount of lithium (approximately 2 mg, mg atom) was required for the blue colour to appear. However, after the addition of an excess of lithium acetate the reaction began again and appeared to proceeded at a normal rate. This experiment provided the 13-deoxy compound **135** (24 mg, 40%), plus other reduction products resulting from the reduction of the 7-methyl ester function.

Methyl *ent*-12β,13-di(methoxymethoxy)-19-oxo-1β,20-cyclo-19,20-cyclogibberellan-7-oate (**161**) and (**162**)



(**155**) (**161**) : (**162**) 3:1 mixture of isomers

Compound **155** (30 mg, 0.07 mmol) was dissolved in ethyl acetate (10 ml), rhodium on alumina (5%, 15 mg) was added and the reaction was placed under an atmosphere of hydrogen and left stirring overnight. Next morning the reaction was diluted with ethyl acetate (20 ml) and filtered through a pad of celite. The solvent was removed *in vacuo* to yield compounds **161** and **162** in quantitative yield. A 3:1 mixture of the endo : exo isomers was formed.

17-endo-methyl isomer (161)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (3H, s, H18), 0.98 (3H, d, J = 6.7 Hz, H17), 0.80 - 2.50 (14H, m), 2.43 (1H, d, J = 8.2 Hz, H5), 2.61 (1H, d, J = 8.2 Hz, H6), 3.30, 3.36 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.39 (1H, m, H12), 3.70 (3H, s, -CO_2CH_3), 4.54, 4.84 (2x1H, ABd, J = 7.3 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.56, 4.67 (2x1H, ABd, J = 6.7 Hz, 13-$OC\underline{H}_2OCH_3$†).

^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3 (C18), 17.4 (C2), 18.4 (C17), 26.2 (C11), 29.6 (C1), 32.2 (-CO$\underline{C}$H-), 36.0 (C14), 38.4 (C16), 38.5 (C3), 43.2 (C10 and C9 overlapped), 45.1 (C15), 48.0 (C4), 51.2 (C6), 51.7 (-$CO_2\underline{C}H_3$), 51.8 (C5), 52.5 (C8), 55.5, 55.7 (13-$OCH_2O\underline{C}H_3$, 12-$OCH_2O\underline{C}H_3$), 80.7 (C12), 84.7 (C13), 94.3 (13-O$\underline{C}H_2OCH_3$), 96.8 (12-O$\underline{C}H_2OCH_3$), 174.6 (C7), 214.6 (C19).

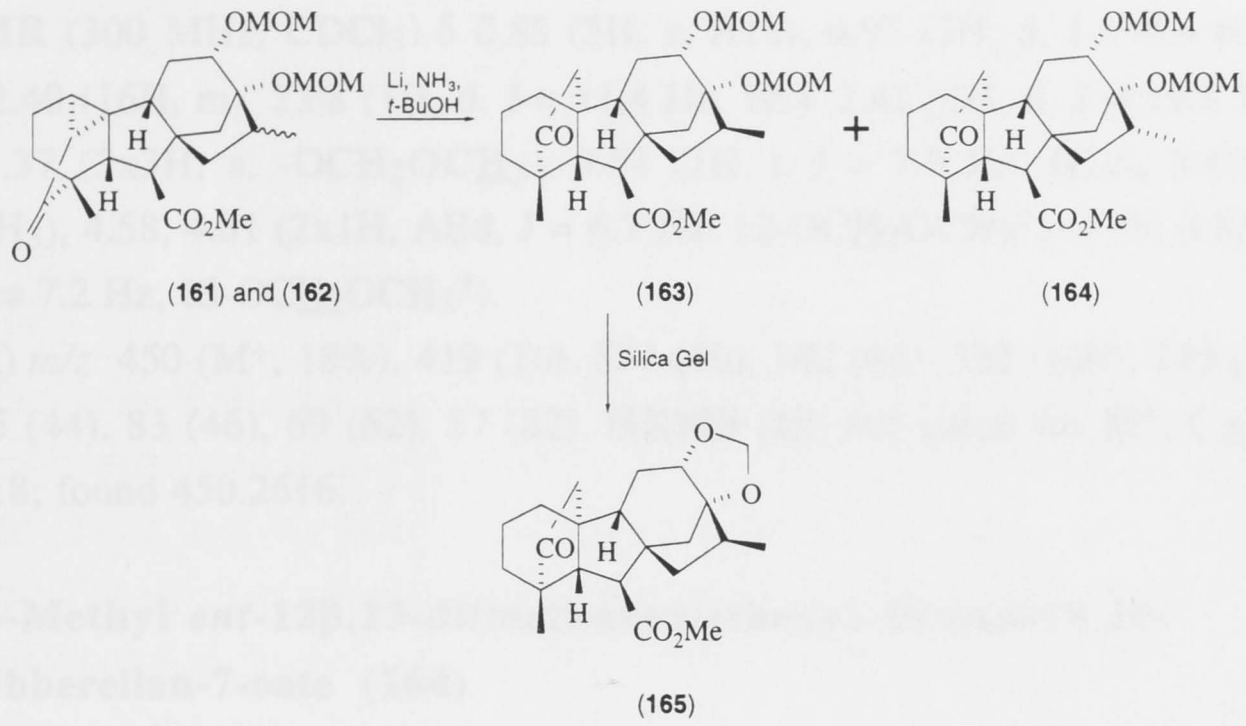
MS (EI) *m/z* 448 (M^+, 51%), 417 (36), 372 (98), 340 (72), 312 (62), 283 (47), 205 (60), 175 (67), 148 (100), 110 (82), 91 (65), 69 (84). **HRMS** (EI) *m/z* calcd for M^+, $C_{25}H_{36}O_7$: 448.2461; found 448.2460.

17-exo-methyl isomer (162)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, s, H18), 1.02 (3H, d, J = 7.4 Hz, H17), 0.80 - 2.50 (14H, m), 2.43 (1H, d, J = 8.0 Hz, H5), 2.53 (1H, d, J = 8.0 Hz, H6), 3.32, 3.36 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.60 (1H, m, H12), 3.70 (3H, s, -CO_2CH_3), 4.54, 4.67 (2x1H, ABd, J = 6.8 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.58, 4.76 (2x1H, ABd, J = 6.0 Hz, 13-$OC\underline{H}_2OCH_3$†).

^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 (C17), 15.3 (C18), 17.4 (C2), 25.5 (C11), 29.3 (C1), 32.6 (-CO$\underline{C}$H-), 36.0 (C14), 38.8 (C16), 38.8 (C3), 39.0 (C10), 44.8 (C15), 45.2 (C9), 48.0 (C4), 51.6 (C6), 51.7 (-$CO_2\underline{C}H_3$), 52.2 (C5), 53.1 (C8), 55.0, 55.4 (13-$OCH_2O\underline{C}H_3$, 12-$OCH_2O\underline{C}H_3$), 75.0 (C12), 85.7 (C13), 92.5 (13-O$\underline{C}H_2OCH_3$), 96.8 (12-O$\underline{C}H_2OCH_3$), 174.6 (C7), 214.6 (C19).

Methyl *ent*-12β,13-di(methoxymethoxy)-19-oxo-19,20-cyclogibberellan-7-oate (**163**) and (**164**)



Compounds **161** and **162** (30 mg, 0.07 mmol) were dissolved in dry THF (2.0 ml) together with *t*-butyl alcohol (30 µl, 0.31 mmol). After cooling to -78°C, liquid ammonia (approximately 15 ml) was distilled into the flask from a sodium amide solution. Lithium metal (approximately 1 - 2 mg, 0.20 - 0.4 mg atom, approximately 2 eq) was added in small pieces with vigorous stirring. The reaction was quenched with saturated ammonium chloride solution (5 ml), upon the appearance of a deep blue colour that persisted for 30 sec. The ammonia was then allowed to evaporate under a gentle flow of nitrogen. The white solid residue was dissolved in water (10 ml) and ethyl acetate (50 ml), the layers were separated and the aqueous layer was extracted with ethyl acetate (2x10 ml). The combined organic phases were washed with brine (15 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo* to yield a yellow oil. The residue was dissolved in dichloromethane (10 ml) and treated with Dess-Martin periodinane (100 mg, 0.24 mmol, 2 eq). After 15 min, when TLC analysis indicated that the reaction was complete, sat. sodium bicarbonate solution containing 7% sodium thiosulfate (20 ml) was added and the reaction mixture was left stirring until the cloudiness had dissipated. The reaction mixture was diluted with ethyl acetate (60 ml), the layers were separated and the organic phase was washed with sat. sodium bicarbonate solution (10 ml), brine (10 ml) and the combined aqueous phases were back-extracted with ethyl acetate (2x20 ml). The combined organic phases were dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. ^{1}H NMR spectroscopy revealed a 3:1 mixture of the di(methoxymethyl) compounds **163** and **164**.

17-endo-Methyl *ent*-12β,13-di(methoxymethoxy)-19-oxo-19,20-cyclogibberellan-7-oate (163).

R_f : 0.36 (hexane:ethyl acetate, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, s, H18), 0.97 (3H, d, J = 6.6 Hz, H17), 0.80 - 2.40 (16H, m), 2.08 (1H, d, J = 11.8 Hz, H5), 2.42 (1H, d, J = 11.8 Hz, H6), 3.35, 3.37 (2x3H, s, $-OCH_2OC\underline{H}_3$), 3.51 (1H, t, J = 7.9 Hz, H12), 3.69 (3H, s, $-CO_2CH_3$), 4.58, 4.81 (2x1H, ABd, J = 6.7 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.59, 4.85 (2x1H, ABd, J = 7.2 Hz, 13-$OC\underline{H}_2OCH_3$†).

MS (EI) *m/z* 450 (M^+, 18%), 419 (16), 374 (60), 342 (66), 332 (100), 243 (36), 129 (48), 95 (44), 83 (46), 69 (62), 57 (82). **HRMS** (EI) *m/z* calcd for M^+, $C_{25}H_{38}O_7$: 450.2618; found 450.2616.

17-exo-Methyl *ent*-12β,13-di(methoxymethoxy)-19-oxo-19,20-cyclogibberellan-7-oate (164).

R_f : 0.36 (hexane:ethyl acetate, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, s, H18), 1.03 (3H, d, J = 7.3 Hz, H17), 0.80 - 2.40 (18H, m), 3.35, 3.37 (2x3H, s, $-OCH_2OC\underline{H}_3$), 3.69 (3H, s, $-CO_2CH_3$), 3.93 (1H, m, H12), 4.61, 4.76 (2x1H, ABd, J = 6.9 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.64, 4.83 (2x1H, ABd, J = 8.4 Hz, 13-$OC\underline{H}_2OCH_3$†).

However, upon chromatography on silica gel (hexane/ethyl acetate, 2:1) the major compound **163** decomposed to form the dioxalane **165**.

17-endo-Methyl *ent*-12β-13-dioxolato-19-oxo-19,20-cyclogibberellan-7-oate (165, 15 mg, 50%).

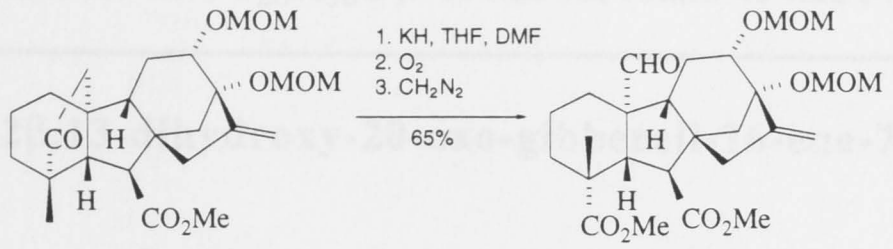
R_f : 0.48 (hexane:ethyl acetate, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, s, H18), 1.02 (3H, d, J = 6.6 Hz, H17), 0.80 - 2.20 (16H, m), 2.36 (1H, d, J = 12.0 Hz, H5), 2.42 (1H, d, J = 12.0 Hz, H6), 3.61 (1H, dd, J_1 = 8.9 Hz, J_2 = 7.1 Hz, H12), 3.70 (3H, s, $-OCH_2OC\underline{H}_3$), 4.87 (1H, s, $-OCH_2O-$), 5.07 (1H, s, $-OCH_2O-$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 17.1 (C18), 18.4 (C17), 19.8 (C2), 25.9 (C11), 36.1 ($-CO\underline{C}H_2-$), 36.3 (C16), 36.6 (C14), 38.0 (C3), 43.4 (C1), 45.7 (C15), 48.5, 48.6 (C10, C4), 51.8 ($-CO_2\underline{C}H_3$), 52.5 (C6), 53.0 (C9), 53.8 (C8), 59.5 (C5), 83.9 (C12), 86.0 (C13), 94.4 ($-OCH_2O-$), 173.4 (C7), 220.0 (C19).

MS (EI) *m/z* 374 (M^+, 28%), 345 (8), 331 (100), 273 (10), 241 (9), 213 (10), 173 (7), 131 (7), 105 (9), 91 (12), 79 (10), 55 (16). **HRMS** (EI) *m/z* calcd for M^+, $C_{22}H_{30}O_5$: 374.2093; found 374.2093.

Dimethyl *ent*-12β,13-di(methoxymethoxy)-20-oxo-gibberell-16-ene-7,19-dioate (166)



(134) (166)

An excess of dry (oil free) potassium hydride (approximately 16.1 mg, 0.40 mmol) was added to a solution of the cyclopentanone **157** (30 mg, 0.067 mmol) in dry THF (2 ml) and dry DMF (2 ml) at 0°C with stirring under an atmosphere of nitrogen. The reaction mixture was left stirring for 2 h, after which time the reaction flask was thoroughly flushed with nitrogen before a steady stream of dry oxygen gas was passed through the solution. After 20 min TLC analysis indicated that the reaction was complete. The reaction was throughly flushed with nitrogen then carefully quenched with methanol (5 ml), and the solvent removed *in vacuo*. The DMF was removed under high vacuum with gentle heating. The solid residue was dissolved in water (20 ml) and ethyl acetate (50 ml), the layers separated, and the aqueous phase extracted with ethyl acetate (2x20 ml). The combined organic phases were washed with brine (10 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. The residue was dissolved in methanol (10 ml) and treated with an excess of diazomethane. After stirring for 10 min the solvent was removed under a gentle stream of nitrogen. Purification on silica gel (hexane/ethyl acetate, 3:1) afforded the desired aldehyde **166** (21.5 mg, 65%) as a colourless oil.

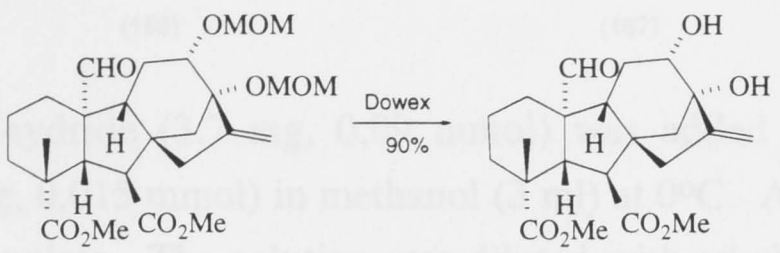
R_f : 0.68 (hexane:ethyl acetate, 1:1). **IR** 1725 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 - 1.10 (2H, m, 1xH1 1xH3), 1.09 (3H, s, H18), 1.20 - 1.75 (5H, m, H9 2xH2 2xH11), 1.90 - 2.10 (2H, m, 2xH14), 2.14 - 2.22 (4H, m, [H5, J = 11.8 Hz] 1xH1 2xH15), 2.30 - 2.45 (1H, m, 1xH3), 3.32, 3.35 (2x3H, s, $-OCH_2OC\underline{H}_3$), 3.60 (1H, m, H12), 3.71, 3.73 (2x3H, s, $-CO_2CH_3$), 3.72 (1H, d, J = 11.8 Hz, H6), 4.51, 4.73 (2x1H, ABd, J = 7.2 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.59, 4.78 (2x1H, ABd, J = 6.7 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.09 (2H, br s, H17), 9.72 (1H, s, H20).

^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (C2), 25.3 (C11), 27.8 (C18), 32.4 (C1), 37.6 (C3), 39.2 (C14), 44.6 (C15 and C4 overlapped), 48.8 (C8), 49.3 (C6), 51.6, 51.8 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 53.8 (C9), 55.4, 55.5 (13-$OCH_2O\underline{C}H_3$, 12-$OCH_2O\underline{C}H_3$), 57.3 (C5), 59.7 (C10), 78.2 (C12), 85.9 (C13), 91.6 (13-$O\underline{C}H_2OCH_3$), 96.2 (12-$O\underline{C}H_2OCH_3$), 109.4 (C17), 149.4 (C16), 175.5, 176.2 (C19, C7), 204.6 (C20).

MS (EI) *m/z* 494 (M^+, 4%), 462 (5), 432 (10), 417 (86), 389 (89), 373 (95), 358 (70), 329 (100), 299 (81), 269 (52), 239 (63), 211 (39), 185 (33), 155 (31) 121 (27) 91 (78). **HRMS** (EI) *m/z* calcd for M^+, $C_{26}H_{38}O_9$: 494.2516; found 494.2514.

Dimethyl *ent*-12β,13-dihydroxy-20-oxo-gibberell-16-ene-7,19-dioate (136)



(166) (136)

Dowex resin (95 mg of wet resin) was added to a solution of the aldehyde **166** (10 mg, 0.020 mmol) in methanol (4.3 ml) and water (0.7 ml). The reaction mixture was then heated under reflux for 48 h, after which time TLC analysis indicated that the reaction was complete. The reaction mixture was cooled, diluted with ethyl acetate (50 ml) and filtered through a pad of celite. The filtrate was then washed with brine (10 ml), dried over sodium sulfate, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 1:1) afforded the desired deprotected aldehyde **136** (7.4 mg 90%).

R_f : 0.30 (hexane:ethyl acetate, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (3H, s, H18), 0.80 - 2.40 (15H, m), 2.18 (1H, d, J = 12.5 Hz, H5), 3.62 (1H, m, H12), 3.66, 3.73 (2x3H, s, -CO_2CH_3), 3.81 (1H, d, J = 12.5 Hz, H6), 5.08 (1H, br s, H17), 5.20 (1H, br s, H'17), 9.68 (1H, s, H20).

^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7 (C2), 27.7 (C11), 28.1 (C18), 32.8 (C1), 37.6 (C3), 41.5 (C14), 44.3 (C4), 44.9 (C15), 48.6 (C8), 49.6 (C6), 51.7, 51.8 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 53.3 (C9), 55.3 (C5), 59.5 (C10), 74.5 (C12), 79.6 (C13), 109.2 (C17), 152.4 (C16), 174.9, 176.4 (C19, C7), 205.7 (C20).

MS (EI) *m/z* 406 (M^+, 5%), 388 (15), 374 (75), 360 (46), 328 (72), 300 (74), 273 (42), 241 (66), 213 (47), 167 (47), 135 (65), 121 (95), 105 (67), 91 (100), 77 (75), 55 (100). **HRMS** (EI) *m/z* calcd for M^+, $C_{22}H_{30}O_7$: 406.1992; found 406.1991.

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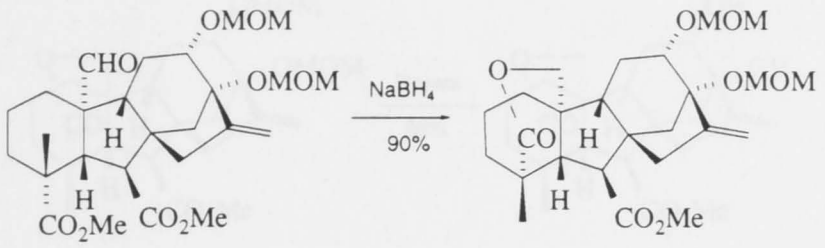
ent-20-Hydroxy-12β,13-di(methoxymethoxy)gibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (167)



(166) (167)

Sodium borohydride (3.7 mg, 0.09 mmol) was added to a solution of the aldehyde **166** (7.7 mg, 0.015 mmol) in methanol (3 ml) at 0°C. After 1 h TLC showed that reaction was complete. The solution was diluted with ethyl actetate (50 ml) and acidified with sodium dihydrogen phosphate solution (20%, 20 ml). The layers were separated and the aqueous phase was extracted with ethyl acetate (2x10 ml). The combined organic phases were washed with brine (2x20 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel afforded the lactone **167** (6.0 mg, 90%) as a colourless oil.

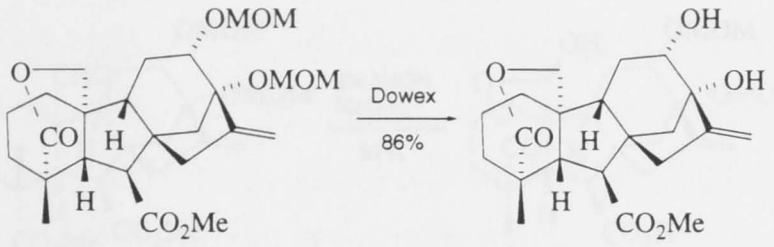
R_f : 0.47 (hexane:ethyl acetate, 1:1). **IR** 1730 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (3H, s, H18), 0.80 - 2.20 (13H, m), 2.14 (1H, d, J = 12.4 Hz, H5), 2.76 (1H, d, J = 12.4 Hz, H6), 3.34, 3.36 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.67 (1H, m, H12), 3.70 (3H, s, -CO_2CH_3), 4.10 (1H, d, J = 13.7 Hz, H20), 4.56 (1H, d, J = 13.7 Hz, H'20), 4.56, 4.72 (2x1H, ABd, J = 7.1 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.67, 4.91 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.17 (2H, br s,H17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (C2), 23.0 (C18), 26.6 (C11), 37.9 (C1), 38.4 (C3), 39.7 (C14), 41.6, 42.6 (C10, C4), 46.1 (C15), 48.4 (C8), 51.3, 51.5 (C6, C5), 52.0 (-$CO_2\underline{C}H_3$), 53.7 (C9), 55.3, 55.5 (13-$OCH_2O\underline{C}H_3$, 12-$OCH_2O\underline{C}H_3$), 74.0 (C20), 79.7 (C12), 85.5 (C13), 91.8 (13-$O\underline{C}H_2OCH_3$), 97.3 (12-$O\underline{C}H_2OCH_3$), 111.2 (C17), 150.3 (C16), 173.4, 175.2 (C19, C7).

MS (EI) *m/z* 433 (M^+-OCH_3, 9%), 419 (100), 403 (8), 387 (30), 359 (12), 329 (11), 297 (11), 269 (18), 253 (13), 225 (18), 211 (12), 135 (11), 105 (15), 91 (18), 71 (19), 57 (25). **HRMS** (EI) *m/z* calcd for M^+-OCH_3, $C_{24}H_{33}O_7$: 433.2226; found 433.2226.

ent-12β,13,20-Trihydroxy-gibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (137)



(167) (137)

Dowex resin (100 mg of wet resin) was added to a solution of the lactone **167** (6 mg, 0.013 mmol) in methanol (6 ml) and water (1.0 ml). The reaction mixture was then heated under reflux for 48 h, after which time TLC analysis indicated that reaction was complete. The reaction mixture was cooled, diluted with ethyl acetate (50 ml) and filtered through a pad of celite. The filtrate was then washed with brine (10 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 2:1-1:2) afforded the desired deprotected lactone **137** (4.2 mg 86%) as an off-white solid.

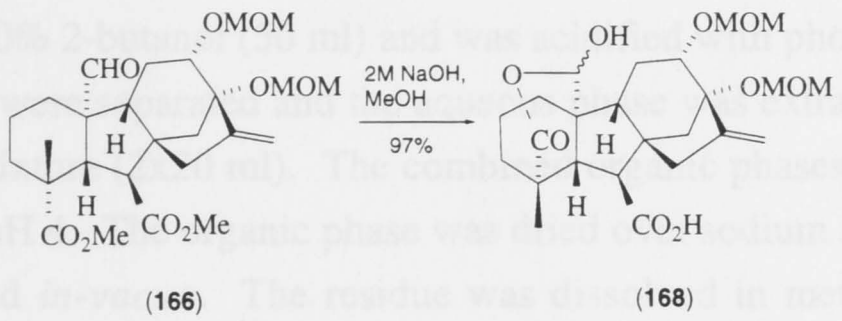
R_f : 0.10 (hexane:ethyl acetate, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (3H, s, H18), 0.80 - 2.20 (15H, m), 2.17 (1H, d, J = 12.6 Hz, H5), 2.79 (1H, d, J = 12.6 Hz, H6), 3.69 (1H, dd, J = 7.6 Hz, H12), 3.71 (3H, s, $-CO_2CH_3$), 4.11 (1H, d, J_{gem} = 12.1 Hz, 20-pro-S-H), 4.43 (1H, dd, J_{gem} = 12.1 Hz, $J_{20,1\beta}$ = 2.3 Hz, 20-pro-R-H), 5.11 (1H, br s, H17), 5.27 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (C2), 23.2 (C18), 27.4 (C11), 38.3 (C1), 39.7 (C3), 41.0 (C14), 41.5 (C10), 42.6 (C4), 45.2 (C15), 48.4 (C8), 51.3 (C6), 52.0 ($-CO_2\underline{C}H_3$), 52.1, 52.8 (C5, C9), 74.1 (C20), 74.6 (C12), 79.1 (C13), 110.2 (C17), 153.2 (C16), 173.1, 175.1 (C19, C7).

MS (EI) *m/z* 376 (M^+, 11%), 344 (13), 316 (13), 286 (9), 269 (64), 226 (100), 198 (22), 149 (9), 134 (13), 121 (17), 95 (15), 81 (20), 60 (18). **HRMS** (EI) *m/z* calcd for M^+, $C_{21}H_{28}O_6$: 376.1886; found 376.1887.

ent-20,20-Dihydroxy-12β,13-di(methoxymethoxy)gibberell-16-ene-7,19-dioic Acid 19,20-Lactone (168)



(166) (168)

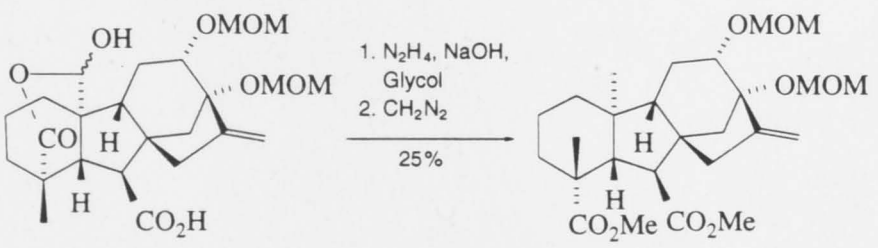
The aldehyde **166** (29 mg, 0.059 mmol) was dissolved in methanol (2.0 ml) and sodium hydroxide solution (2M, 6.0 ml). The reaction mixture was heated at reflux for 24 h. The mixture was diluted with ethyl acetate containing 2-butanol (20%, 50 ml) and was acidified with phosphoric acid (10%, 10 ml). The layers were separated and the aqueous phase was extracted with the ethyl acetate/2-butanol mixture (2x20 ml). The combined organic phases were washed with brine to pH 4. The organic phase was dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Purification on silica gel (hexane/ethyl acetate/acetic acid, 2:1:0.1) provided the hydroxy lactone **168** (26.6 mg, 97%) as a a white solid.

R_f : 0.34 (hexane:ethyl acetate:acetic acid:methanol, 3:1.5:0.2:0.2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (3H, s, H18), 0.80 - 2.50 (18H, m), 2.17 (1H, d, J = 12.5 Hz, H5), 3.34 (3H, s, 13-$OCH_2OC\underline{H}_3$#), 3.37 (4H, s, 12-$OCH_2OC\underline{H}_3$# and H6 overlapped), 3.66 (1H, m, H12), 4.55, 4.74 (2x1H, ABd, J = 7.2 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.68, 4.86 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.15 (2H, br s, H17), (H20 not observed).

MS (EI) *m/z* 465 (M^+-H, 10%), 448 (6), 432 (10), 421 (12), 403 (52), 375 (18), 359 (100), 344 (28), 331 (32), 313 (44), 285 (58), 269 (28), 257 (22) 239 (30).

Dimethyl _ent_-12β,13-di(methoxymethoxy)gibberell-16-ene-7,19-dioate (169)



(168) (169)

Anhydrous hydrazine (0.25 ml) was added to a solution of the hydroxy lactone **168** (26.6 mg, 0.057 mmol) in ethylene glycol (1.5 ml) and the reaction was heated at

100°C for 30 min. Half a pellet of sodium hydroxide (approximately 200 mg) was added and the temperature was raised to 116°C for 1 h. Finally, the temperature was raised to 180°C and the reaction continued overnight. The mixture was cooled, diluted with ethyl acetate/20% 2-butanol (50 ml) and was acidified with phosphoric acid (10%, 10 ml). The layers were separated and the aqueous phase was extracted with the ethyl acetate/2-butanol mixture (2x20 ml). The combined organic phases were washed with brine (3x10 ml) to pH 4. The organic phase was dried over sodium sulfate, filtered and the solvent removed *in-vacuo*. The residue was dissolved in methanol (10 ml) and treated with an excess of diazomethane; after 10 min the solvent was removed under a gentle stream of nitrogen. Purification on silica gel (hexane/ethyl acetate, 3:1) afforded compound **169** (7.1 mg, 25%) as a colourless oil, contaminated with a small amount of gibberellin like impurity (approximately 10%) that could not be separated by chromatography.

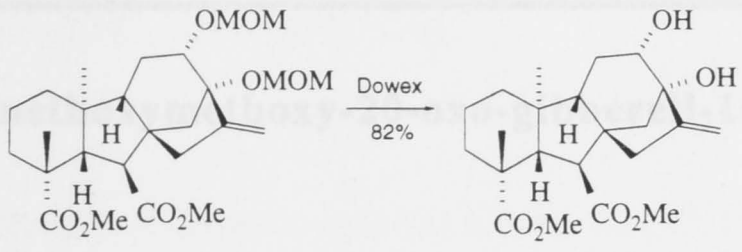
R_f : 0.42 (hexane:ethyl acetate, 3:1). **IR** 1725 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (3H, s, H20), 1.04 (3H, s, H18), 0.80 - 2.40 (13H, m), 1.89 (1H, d, J = 12.0 Hz, H5), 3.34, 3.38 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.42 (1H, d, J = 12.0 Hz, H6), 3.64 (1H, m, H12), 3.67, 3.69 (2x3H, s, -CO_2CH_3), 4.53, 4.73 (2x1H, ABd, J = 7.0 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.68, 4.86 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.09 (2H, br s, H17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7 (C20), 19.4 (C2), 26.0 (C11), 28.0 (C18), 37.7 (C1), 38.9 (C3 and C14 overlapped), 43.6, 44.2 (C4, C10), 45.7 (C15), 48.5 (C8), 50.2 (C6), 51.4, 51.5 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 55.0 (C9), 55.4 (13-$OCH_2O\underline{C}H_3$ and 12-$OCH_2O\underline{C}H_3$ overlapped), 58.3 (C5), 79.6 (C12), 87.0 (C13), 91.7 (13-$O\underline{C}H_2OCH_3$), 96.8 (12-$O\underline{C}H_2OCH_3$), 109.2 (C17), 150.4 (C16), 175.9, 177.4 (C19, C7).

MS (EI) *m/z* 480 (M^+, 6%), 448 (6), 435 (100), 403 (28), 388 (22), 375 (60), 359 (30), 315 (32), 299 (50), 271 (28), 181 (46), 149 (34), 121 (30), 95 (32) 85 (34) 71 (48), 57 (76). **HRMS** (EI) *m/z* calcd for M^+, $C_{26}H_{40}O_8$: 480.2723; found 480.2723.

Dimethyl *ent*-12β,13-dihydroxygibberell-16-ene-7,19-dioate (138)



(169) (138)

Dowex resin (80 mg of wet resin) was added to a solution of the compound **169** (7 mg, 0.014 mmol) in methanol (9 ml) and water (1.6 ml). The reaction mixture was then heated under reflux for 44 h. The reaction mixture was diluted with ethyl acetate (50 ml) and filtered through a pad of celite. The filtrate was then washed with brine (10 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 1:1) afforded compound **138** (4.7 mg 82%) as a solid.

R_f : 0.37 (hexane:ethyl acetate, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72 (3H, s, H20), 1.08 (3H, s, H18), 0.80 - 2.30 (15H, m), 1.87 (1H, d, J = 12.5 Hz, H5), 3.36 (1H, d, J = 12.5 Hz, H6), 3.67 (4H, s, H12 and 7-CO_2CH_3#), 3.70 (3H, s, 19-CO_2CH_3#), 5.04 (1H, br s, H17), 5.19 (1H, br s, H'17).

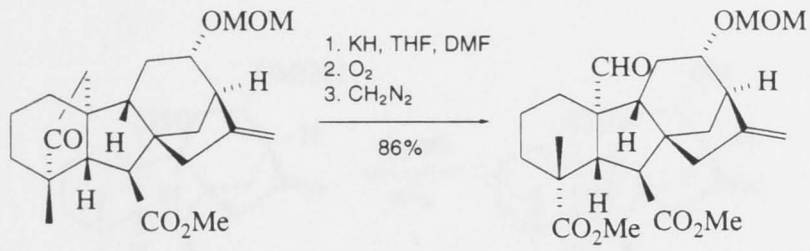
^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6 (C20), 19.6 (C2), 22.7 (C11), 28.9 (C18), 37.6 (C1), 39.5 (C3), 41.4 (C14), 43.8, 44.4 (C4, C10), 45.1 (C15), 48.0 (C8), 50.7 (C6), 51.5 (7-$CO_2\underline{C}H_3$ and 19-$CO_2\underline{C}H_3$ overlapped), 54.2 (C9), 56.9 (C5), 75.0 (C12), 77.4 (C13), 108.7 (C17), 153.8 (C16), 175.3, 177.5 (C19, C7).

MS (EI) *m/z* 392 (M^+, 9%), 360 (51), 332 (68), 318 (28), 300 (22), 272 (25), 255 (16), 213 (23), 181 (32), 149 (26), 121 (42), 97 (36), 83 (41), 71 (59) 57 (100).

HRMS (EI) *m/z* calcd for M^+, $C_{22}H_{32}O_6$: 392.2199; found 392.2198.

7.5.3 12α-MONOHYDROXY SERIES

Dimethyl *ent*-12β-methoxymethoxy-20-oxo-gibberell-16-ene-7,19-dioate (170)



(135) (170)

An excess of dry (oil free) potassium hydride (approximately 16.1 mg, 0.40 mmol) was added to a solution of the cyclopentanone **158** (28 mg, 0.072 mmol) in dry THF (3 ml) and dry DMF (3 ml) at 0°C, stirring under an atmosphere of nitrogen. After 2 h the reaction flask was thoroughly flushed with nitrogen before a steady stream of dry oxygen gas was passed through the solution. After 20 min TLC analysis indicated that the reaction was complete. The reaction mixture was carefully quenched with methanol (5 ml), and the solvent was removed *in vacuo*. The DMF was removed under high vacuum with gentle heating. The solid residue was dissolved in water (20 ml) and ethyl acetate (50 ml), the layers separated and the aqueous phase extracted with ethyl acetate (2x20 ml). The combined organic phases were washed with brine (10 ml), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. The residue was dissolved in methanol (10 ml) and treated with an excess of diazomethane, after 10 min, the solvent was removed under a gentle stream of nitrogen. Purification on silica gel (hexane/ethyl acetate, 3:1) afforded the desired aldehyde **170** (27 mg, 86%) as an oil.

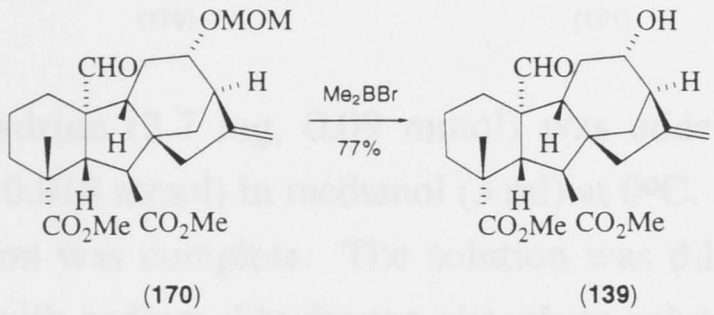
R_f : 0.85 (hexane:ethyl acetate, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, s, H18), 0.86 - 2.40 (13H, m), 2.21 (1H, d, J = 12.7 Hz, H5), 2.70 (1H, d, J = 4.5 Hz, H13), 3.31 (3H, s, $-OCH_2OC\underline{H}_3$), 3.56 (1H, dd, J = 7.1 Hz, H12), 3.62, 3.72 (2x3H, s, $-CO_2CH_3$), 3.92 (1H, d, J = 12.7 Hz, H6), 4.56, 4.65 (2x1H, ABd, J = 6.9 Hz, $-OC\underline{H}_2OCH_3$), 4.97 (1H, br s, H17), 5.00 (1H, br s, H'17), 9.64 (1H, s, H20).

^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7 (C2), 26.2 (C11), 28.1 (C18), 32.8 (C1), 34.2 (C3), 37.7 (C14), 45.2 (C4), 46.3 (C15), 46.5 (C13), 49.7 (C8), 49.9 (C6), 51.6, 51.7 ($7\text{-}CO_2\underline{C}H_3$, $19\text{-}CO_2\underline{C}H_3$), 52.8 (C9), 55.3 ($-OCH_2O\underline{C}H_3$), 56.0 (C5), 59.8 (C10), 79.2 (C12), 94.6 ($-O\underline{C}H_2OCH_3$), 109.2 (C17), 150.9 (C16), 174.8, 176.4 (C19, C7), 205.0 (C20).

MS (EI) *m/z* 434 (M^+-CH_3OH, 3%), 402 (25), 358 (17), 342 (28), 312 (92), 284 (100), 253 (21), 225 (55), 197 (32), 119 (30), 105 (32). **HRMS** (EI) *m/z* calcd for M^+-CH_3OH, $C_{23}H_{30}O_6$: 402.2042; found 402.2044.

Dimethyl *ent*-12β-hydroxy-20-oxo-gibberell-16-ene-7,19-dioate (139)



(170) (139)

The aldehyde **170** (4.3 mg, 0.010 mmol) was dissolved in dry dichloromethane (1 ml) under at atmosphere of nitrogen. The solution was cooled to -78°C with an acetone/dry ice bath and treated with dimethylboron bromide (approximately 50 µl, 0.51 mmol). After 4 min at -78°C the solution was quickly transferred to a vigorously stirred mixture of dichloromethane (5 ml) and sat. sodium bicarbonate solution (5 ml). After 5 min, the solution was diluted with ethyl acetate (25 ml), and acidified with phosphoric acid (10%, 25 ml). The layers were separated, and the organic phase was washed with brine (2x10 ml). The combined aqueous phases were extracted with ethyl acetate (2x20 ml). The combined organic phases were dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 2:1) afforded the desired deprotected aldehyde **139** (3.0 mg, 77%) as a pale yellow solid.

R_f : 0.69 (hexane:ethyl acetate, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (3H, s, H18), 0.80 - 2.40 (14H, m), 2.23 (1H, d, J = 12.7 Hz, H5), 2.60 (1H, d, J = 4.5 Hz, H13), 3.64 (3H, s, 7-CO_2CH_3#), 3.73 (4H, m, 19-CO_2CH_3# and H12 overlapped), 3.95 (1H, d, J = 12.7 Hz, H6), 4.97 (1H, br s, H17), 5.03 (1H, br s, H'17), 9.68 (1H, s, H20).

^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (C2), 28.1 (C18), 28.5 (C11), 33.0 (C1), 34.0 (C3), 37.7 (C14), 45.2 (C4), 46.3 (C15), 49.5 (C13), 49.8 (C8), 50.0 (C6), 51.7, 51.8 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 53.2 (C9), 56.1 (C5), 59.9 (C10), 74.5 (C12), 109.1 (C17), 150.7 (C16), 174.8, 176.5 (C19, C7), 205.4 (C20).

MS (EI) *m/z* 372 (M^+-H_2O, 7%), 358 (25), 326 (25), 312 (66), 284 (100), 253 (20), 225 (63), 199 (24), 183 (24), 155 (28), 129 (26), 105 (31), 91 (40), 79 (28), 57 (52). **HRMS** (EI) *m/z* calcd for M^+, $C_{22}H_{30}O_6$: 390.2042; found 390.2043.

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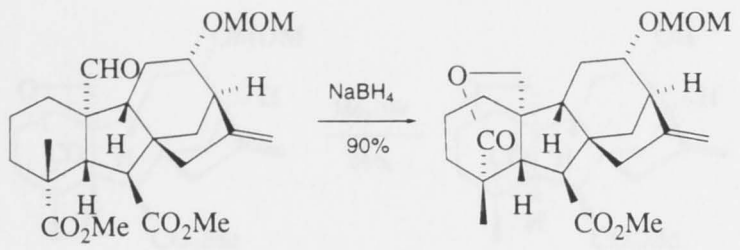
ent-20-Hydroxy-12β-methoxymethoxy-gibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (171)



(170) (171)

Sodium borohydride (3.7 mg, 0.09 mmol) was added to a solution of the aldehyde **170** (8.0 mg, 0.018 mmol) in methanol (3 ml) at 0°C. After 1 h TLC analysis showed that the reaction was complete. The solution was diluted with ethyl acetate (50 ml) and acidified with sodium dihydrogen phosphate solution (20%, 20 ml). The layers were separated and the aqueous phase was extracted with ethyl acetate (2x10 ml). The combined organic phases were washed with brine (2x20 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 3:1) afforded the lactone **171** (2.9mg, 90%) as an oil.

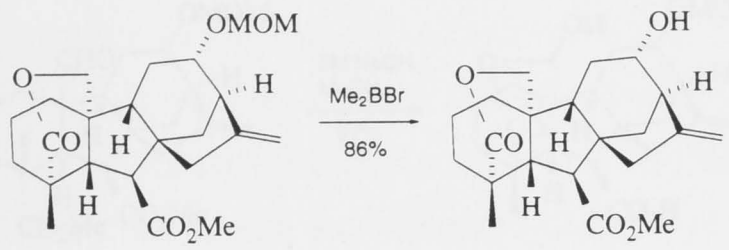
R_f : 0.57 (hexane:ethyl acetate, 2:1). **IR** 1730 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (3H, s, H18), 0.80 - 2.10 (13H, m), 2.17 (1H, d, J = 12.6 Hz, H5), 2.73 (1H, d, J = 4.4 Hz, H13), 2.79 (1H, d, J = 12.6 Hz, H6), 3.36 (3H, s, $-OCH_2OC\underline{H}_3$), 3.60 (1H, m, H12), 3.69 (3H, s, $-CO_2CH_3$), 4.10 (1H, d, J_{gem} = 12.1 Hz, 20-pro-S-H), 4.44 (1H, dd, J_{gem} = 12.1 Hz, $J_{20,1\beta}$ = 2.3 Hz, 20-pro-R-H), 4.62, 4.72 (2x1H, ABd, J = 6.8 Hz, $-OC\underline{H}_2OCH_3$), 4.99 (1H, br s, H17), 5.17 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7 (C2), 23.3 (C18), 26.1 (C11), 34.3 (C1), 38.3 (C3), 39.9 (C14), 41.6 (C10), 42.7 (C4), 46.4 (C15), 46.8 (C13), 49.9 (C8), 51.6, 51.9 (C5, C6), 51.8 ($-CO_2\underline{C}H_3$), 53.0 (C9), 55.4 ($-OCH_2O\underline{C}H_3$), 74.2 (C20), 79.9 (C12), 94.9 ($-O\underline{C}H_2OCH_3$), 109.7 (C17), 150.8 (C16), 173.4, 175.1 (C19, C7).

MS (EI) *m/z* 404 (M^+, 20%), 372 (53), 344 (34), 326 (25), 312 (32), 299 (23), 284 (38), 269 (24), 237 (25), 225 (29), 197 (29), 155 (36), 131 (32), 119 (43), 105 (47), 91 (52), 57 (100). **HRMS** (EI) *m/z* calcd for M^+, $C_{23}H_{32}O_6$: 404.2199; found 404.2199.

ent-12β,20-Dihydroxy-gibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (140)



(171) (140)

The lactone **171** (5.9 mg, 0.015 mmol) was dissolved in dry dichloromethane (1 ml) under at atmosphere of nitrogen. The solution was cooled to -78°C and treated with dimethylboron bromide (approximately 50 µl, 0.51 mmol). After 4 min at -78°C the solution was quickly transferred to a vigorously stirred mixture of dichloromethane (5 ml) and sat. sodium bicarbonate solution (5 ml). After 5 min, the solution was diluted with ethyl acetate (25 ml) and acidified with phosphoric acid (10%, 25 ml). The layers were separated and the organic phase was washed with brine (2x10 ml). The combined aqueous phases were extracted with ethyl acetate (2x20 ml). The combined organic phases were dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 2:1) afford the desired deprotected lactone **140** (4.6 mg, 86%) as an oil, contaminated with a small amount of an impurity that could not be separated by chromatography.

R_f : 0.28 (hexane:ethyl acetate, 1:1).

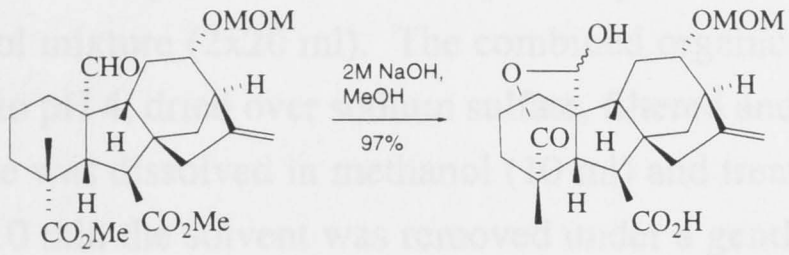
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (3H, s, H18), 0.80 - 2.10 (14H, m), 2.18 (1H, d, J = 12.6 Hz, H5), 2.60 (1H, d, J = 4.9 Hz, H13), 2.80 (1H, d, J = 12.6 Hz, H6), 3.69 (3H, s, $-CO_2CH_3$), 3.76 (1H, dd, J = 8.0 Hz, H12), 4.10 (1H, d, J_{gem} = 12.1 Hz, 20-pro-S-H), 4.44 (1H, dd, J_{gem} = 12.1 Hz, $J_{20,1\beta}$ = 2.2 Hz, 20-pro-R-H), 4.98 (1H, br s, H17), 5.06 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7 (C2), 23.3 (C18), 27.1 (C11), 34.0 (C1), 38.3 (C3), 39.8 (C14), 41.5 (C10), 42.7 (C4), 46.5 (C15), 49.8 (C8), 50.4 (C13), 51.5 ($-CO_2\underline{C}H_3$), 51.9 (C5 and C6 overlapped), 53.0 (C9), 74.2 (C20), 75.1 (C12), 109.6 (C17), 150.6 (C16), 173.4, 175.2 (C19, C7).

MS (EI) *m/z* 360 (M^+, 31%), 328 (22), 314 (15), 300 (47, 282 (37), 255 (43), 237 (100), 211 (18), 183 (17), 155 (19), 129 (18), 105 (25), 91 (33), 79 (23), 55 (23).

HRMS (EI) *m/z* calcd for M^+, $C_{21}H_{28}O_5$: 360.1937; found 360.1936.

ent-20,20-Dihydroxy-12β-methoxymethoxygibberell-16-ene-7,19-dioic Acid 19,20-Lactone (172)



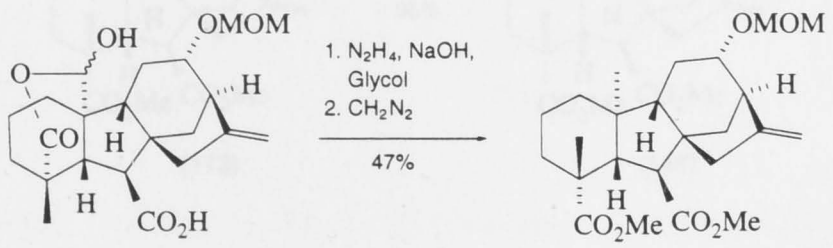
(170) (172)

The aldehyde **170** (46 mg, 0.105 mmol) was dissolved in methanol (2.0 ml) and sodium hydroxide solution (2M, 5.5 ml). The reaction mixture was heated at reflux for 12 h, cooled, diluted with ethyl acetate containing 2-butanol (20%, 50 ml) and was acidified with phosphoric acid (10%, 10 ml). The layers were separated and the aqueous phase was extracted with the ethyl acetate/2-butanol mixture (2x20 ml). The combined organic phases were washed with brine to pH 4, and the organic phase was dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Purification on silica gel (hexane/ethyl acetate/acetic acid, 2:1:0.1) provided the hydroxy lactone **172** (41.7 mg, 97%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, s, H18), 0.80 - 2.50 (15H, m), 1.90 (1H, d, J = 13.1 Hz, H5), 2.74 (1H, m, H13), 3.37 (4H, s, -$OCH_2O\underline{C}H_3$ and H6 overlapped), 3.62 (1H, m, H12), 4.65, 4.74 (2x1H, ABd, J = 6.8 Hz, -$OC\underline{H}_2OCH_3$), 5.00 (1H, br s, H17), 5.04 (1H, br s, H'17), 6.00 (1H , unresolved singlet, H20).

MS (EI) *m/z* 406 (M^+-H, 4%), 344 (79), 298 (71), 270 (100), 225 (47), 183 (37), 143 (42), 119 (55), 105 (76), 91 (90), 71 (71). **HRMS** (EI) *m/z* calcd for M^+, $C_{22}H_{30}O_7$: 406.1992; found 406.1991.

Dimethyl _ent_-12β-methoxymethoxygibberell-16-ene-7,19-dioate (173)



(172) (173)

Anhydrous hydrazine (0.50 ml) was added to a solution of the hydroxy lactone **172** (41.7 mg, 0.102 mmol) in ethylene glycol (3.0 ml) and the reaction was heated at 100°C for 30 min. Two small pellets of sodium hydroxide (approximately 400 mg) were added and the temperature was raised to 116°C for 1 h. Finally, the temperature was

raised to 180°C and the reaction continued overnight. The mixture was cooled, diluted with ethyl acetate/20% 2-butanol (50 ml) and was acidified with phosphoric acid (10%, 10 ml). The layers were separated and the aqueous phase was extracted with the ethyl acetate/2-butanol mixture (2x20 ml). The combined organic phases were washed with brine (3x10 ml) to pH 4, dried over sodium sulfate, filtered and the solvent removed *in vacuo*. The residue was dissolved in methanol (10 ml) and treated with an excess of diazomethane, after 10 min the solvent was removed under a gentle stream of nitrogen. Purification on silica gel (hexane/ethyl acetate, 3:1) afforded compound **173** (21.0 mg, 47%) as a colourless oil,

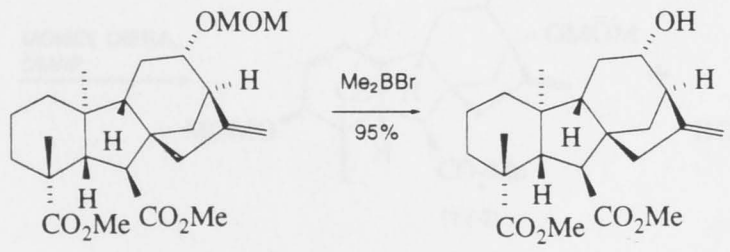
R_f : 0.53 (hexane:ethyl acetate, 4:1). **IR** 1720 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.68 (3H, s, H20), 1.10 (3H, s, H18), 0.80 - 2.40 (13H, m), 1.88 (1H, d, J = 12.7 Hz, H5), 2.69 (1H, d, J = 4.9 Hz, H13), 3.32 (1H, d, J = 12.7 Hz, H6), 3.36 (3H, s, $-OCH_2OC\underline{H}_3$), 3.60 (1H, m, H12), 3.66, 3.68 (2x3H, s, $-CO_2CH_3$), 4.64, 4.72 (2x1H, ABd, J = 6.8 Hz, $-OC\underline{H}_2OCH_3$), 4.94 (1H, br s, H17), 4.98 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 15.1 (C20), 19.7 (C2), 25.9 (C11), 29.4 (C18), 33.9 (C1), 37.6 (C3), 39.9 (C14), 43.8, 44.5 (C4, C10), 46.5 (C15), 46.9 (C13), 49.1 (C8), 51.1 (C6), 51.4 (7-$CO_2\underline{C}H_3$ and 19-$CO_2\underline{C}H_3$ overlapped), 53.4 (C9), 55.3 (12-$OCH_2O\underline{C}H_3$), 56.5 (C5), 80.2 (C12), 94.7 (12-$O\underline{C}H_2OCH_3$), 108.4 (C17), 152.1 (C16), 175.3, 177.7 (C19, C7).

MS (EI) *m/z* 388 (M^+ - CH_3OH, 80%), 360 (33), 328 (63), 300 (78), 239 (53), 209 (46), 181 (100), 149 (38), 121 (50), 107 (61), 91 (40), 79 (29). **HRMS** (EI) *m/z* calcd for M^+ - CH_3OH, $C_{23}H_{32}O_5$: 388.2250; found 388.2231.

Dimethyl *ent*-12β-hydroxygibberell-16-ene-7,19-dioate (141)



(173) (141)

Compound **173** (10.0 mg, 0.023 mmol) was dissolved in dry dichloromethane (1.5 ml) under at atmosphere of nitrogen. The solution was cooled to -78°C and treated with dimethylboron bromide (approximately 100 µl, 1.0 mmol). After 4 min at -78°C the solution was quickly transferred to a vigorously stirred mixture of dichloromethane (5 ml) and sat. sodium bicarbonate solution (5 ml). After 5 min, the solution was diluted with ethyl acetate (25 ml) and acidified with phosphoric acid (10%, 25 ml). The layers

were separated and the organic phase was washed with brine (2x10 ml). The combined aqueous phases were extracted with ethyl acetate (2x20 ml). The combined organic phases were dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 2:1) afford the desired alcohol **141** (8.5 mg, 95%) as an off white solid.

$\mathbf{R_f}$: 0.23 (hexane:ethyl acetate, 3:1). **IR** 1715 cm^{-1}.

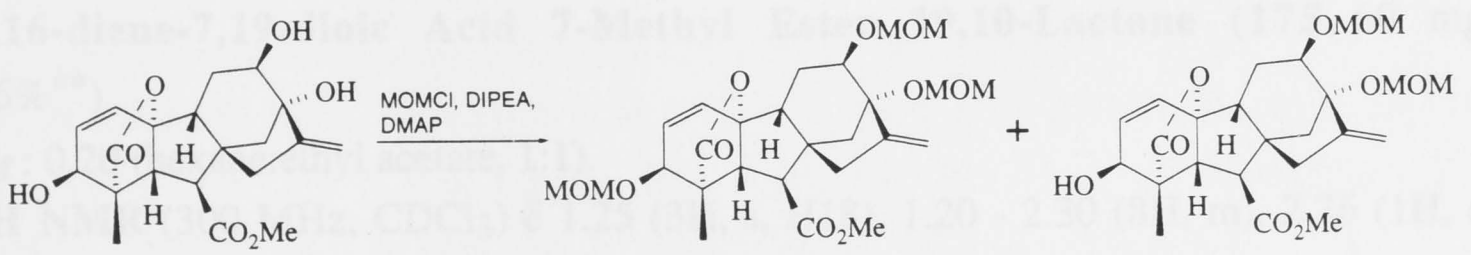
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.68 (3H, s, H20), 1.10 (3H, s, H18), 0.80 - 2.30 (14H, m), 1.88 (1H, d, J = 12.7 Hz, H5), 2.56 (1H, d, J = 4.9 Hz, H13), 3.32 (1H, d, J = 12.7 Hz, H6), 3.67, 3.69 (2x3H, s, $-CO_2CH_3$), 3.45 (1H, m, H12), 4.93 (1H, br s, H17), 5.01 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 15.1 (C20), 19.7 (C2), 28.3 (C11), 29.4 (C18), 33.7 (C1), 37.3 (C3), 39.9 (C14), 43.8, 44.5 (C4, C10), 46.6 (C15), 49.1 (C8), 50.3 (C13), 51.1 (C6), 51.4 (7-$CO_2\underline{C}H_3$ and 19-$CO_2\underline{C}H_3$ overlapped), 53.5 (C9), 56.6 (C5), 75.3 (C12), 108.3 (C17), 151.9 (C16), 175.3, 177.7 (C19, C7).

MS (EI) *m/z* 344 (M^+ - CH_3OH, 3%), 316 (100), 298 (23), 284 (12), 257 (18), 239 (20), 197 (14), 181 (22), 121 (15), 107 (24), 91 (21), 79 (15). **HRMS** (EI) *m/z* calcd for M^+ - CH_3OH, $C_{21}H_{28}O_4$: 344.1988; found 344.1986.

8.5.4 12β,13-DIHYDROXY SERIES

ent-10β-Hydroxy-3α,12α,13-tri(methoxymethoxy)-20-norgibberell-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (174)



DIPEA (1.60 ml, 9.2 mmol, 12.6 eq), a catalytic amount of DMAP, followed by MOMCl (0.70 ml, 9.1 mmol, 12.5 eq) was added to a solution of compound **42** (270 mg, 0.73 mmol) in dry dichloromethane (30 ml) at 0°C under an atmosphere of nitrogen. The reaction mixture was left to warm to room temperature. After 4 days TLC analysis indicated that a mixture of the desired product **174** plus the monohydroxy compound **175** had formed. Sat. sodium bicarbonate solution (20 ml) was added and the reaction was left stirring for 20 min. The layers were separated and the aqueous

phase was back extracted with dichloromethane (2x20 ml). The combined organic phases were washed with hydrochloric acid (1M, 2x20 ml), brine (2x20ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatograhy on silica gel (hexane/ethyl acetate 2:1 - 1:1) afforded in order of elution:

***ent*-10β-Hydroxy-3α,12α,13-tri(methoxymethoxy)-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone** (**174**, 230 mg, 62%, as a colourless oil)

R_f : 0.58 (hexane:ethyl acetate, 1:1). **IR** 1775, 1735 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (3H, s, H18), 1.50 - 2.40 (7H, m), 2.74 (1H, d, J = 10.3 Hz, H6), 3.31 (1H, d, J = 10.3 Hz, H5), 3.36, 3.38, 3.39 (3x3H, s, $-OCH_2OC\underline{H}_3$), 3.74 (3H, s, $-CO_2CH_3$), 4.01 (1H, d, J = 3.6 Hz, H3), 4.22 (1H, m, H12), 4.54, 4.80 (2x1H , ABd, J = 7.2 Hz, $12-OC\underline{H}_2OCH_3$†), 4.67, 4.86 (2x1H, ABd, J = 6.6 Hz, $13-OC\underline{H}_2OCH_3$†), 4.68, 4.73 (2x1H, ABd, J = 6.9 Hz, $3-OC\underline{H}_2OCH_3$†), 5.16 (1H, br s, H17), 5.27 (1H, br s, H'17), 5.94 (1H, dd, J_1 = 8.8 Hz, J_2 = 3.6 Hz, H2), 6.31 (1H, d, J = 8.8 Hz, H1).

^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4 (C18), 25.9 (C11), 42.2 (C14), 43.4 (C15), 48.7 (C9), 50.1 (C8), 50.4 (C6), 52.1 ($-CO_2\underline{C}H_3$), 53.2 (C4), 53.8 (C5), 55.3, 55.4, 55.7 ($12-OCH_2O\underline{C}H_3$, $3-OCH_2O\underline{C}H_3$, $13-OCH_2O\underline{C}H_3$), 75.0 (C3), 78.2 (C12), 86.8 (C13), 90.4 ($13-O\underline{C}H_2OCH_3$), 91.5 (C10), 96.1, 96.8 ($12-O\underline{C}H_2OCH_3$, $3-O\underline{C}H_2OCH_3$), 112.8 (C17), 131.3 (C1), 132.1 (C2), 144.5 (C16), 172.4, (C7), 178.1 (C19).

MS (EI) *m/z* 508 (M^+, 4%), 477 (26), 463 (30), 446 (28), 420 (22), 401 (30), 375 (32), 357 (52), 325 (78), 313 (38), 295 (46), 267 (90), 253 (54), 235 (52), 223 (62), 209 (100). **HRMS** (EI) *m/z* calcd for M^+, $C_{26}H_{36}O_{10}$: 508.2308; found 508.2308.

***ent*-3α,10β-Dihydroxy-12α,13-di(methoxymethoxy)-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone** (**175**, 60 mg, 16%**)

R_f : 0.20 (hexane:ethyl acetate, 1:1).

^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (3H, s, H18), 1.20 - 2.30 (8H, m), 2.76 (1H, d, J = 10.3 Hz, H6), 3.21 (1H, d, J = 10.3 Hz, H5), 3.35, 3.38, (2x3H, s, $-OCH_2OC\underline{H}_3$), 3.73 (3H, s, $-CO_2CH_3$), 4.15 (1H, d, J = 3.6 Hz, H3), 4.21 (1H, dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, H12), 4.54, 4.80 (2x1H, ABd, J = 7.1 Hz, $12-OC\underline{H}_2OCH_3$†), 4.66, 4.85 (2x1H, ABd, J = 6.5 Hz, $13-OC\underline{H}_2OCH_3$†), 5.16 (1H, br s, H17), 5.27 (1H, br s, H'17), 5.90 (1H, dd, J_1 = 9.2 Hz, J_2 = 3.6 Hz, H2), 6.32 (1H, d, J = 9.2 Hz, H1).

^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3 (C18), 25.9 (C11), 42.3 (C14), 43.4 (C15), 48.8 (C9), 50.2 (C6), 50.4 (C8), 52.2 ($-CO_2\underline{C}H_3$), 53.3 (C5), 53.4 (C4), 55.4, 55.4 ($12-OCH_2O\underline{C}H_3$, $13-OCH_2O\underline{C}H_3$), 69.8 (C3), 78.3 (C12), 86.8 (C13), 90.5

(13-O$\underline{C}H_2OCH_3$), 91.6 (C10), 96.1 (12-O$\underline{C}H_2OCH_3$), 113.0 (C17), 132.5 (C1), 132.5 (C2), 144.4 (C16), 172.6 (C7), 178.3 (C19).

** This material could be recycled

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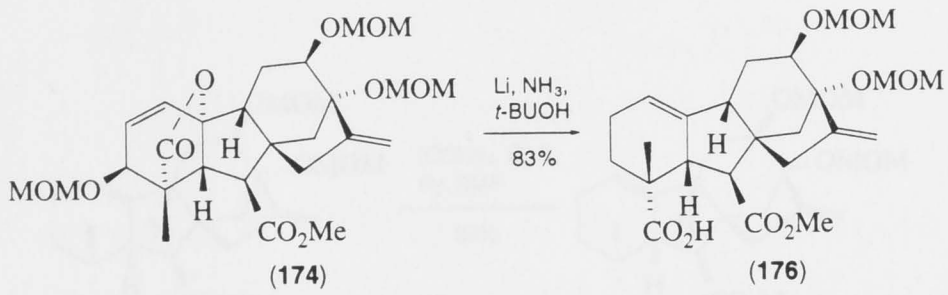
ent-12α,13-Di(methoxymethoxy)-20-norgibberella-1(10),16-diene-7,19-dioic Acid 7-Methyl Ester (176)



(174) (176)

Compound **174** (310 mg, 0.61 mmol) was dissolved in dry THF (5 ml) containing *t*-butyl alcohol (500 µl, 5.3 mmol, 8.7 eq). After cooling to -78°C, liquid ammonia (approximately 120 ml) was distilled into the flask from a sodium amide solution. Lithium metal (approximately 20 mg, 3.0 mg atom) was added in small pieces with vigorous stirring. The reaction was quenched with saturated ammonium chloride solution (5 ml) upon the appearance of a deep blue colour. The ammonia was allowed to evaporate under a gentle flow of nitrogen. The white solid residue was dissolved in ethyl acetate (50 ml) and acidified with phosphoric acid (10%, 20 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (2x10 ml). The combined organic phases were washed with brine (3x15 ml) until pH 4, dried over sodium sulfate, filtered, and the solvent removed *in vacuo* to yield a yellow oil. Chromatography (hexane/ethyl acetate/acetic acid, 2:1:0.1) afforded the acid **176** (228 mg, 83%) as a colourless oil.

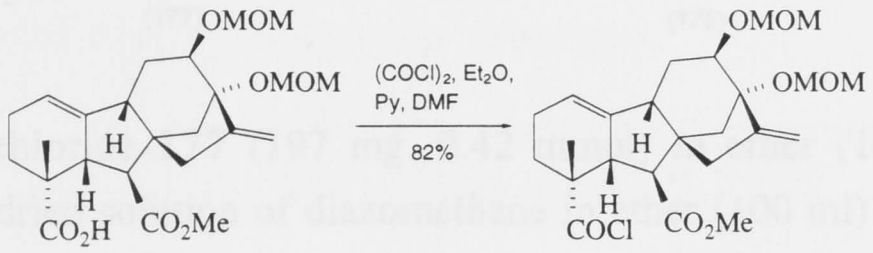
R_f : 0.60 (hexane:ethyl acetate:acetic acid, 1:1:0.1). **IR** 1730 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, s, H18), 0.85 - 2.65 (12H, m), 2.83 (1H, br s, H5), 3.09 (1H, d, J = 5.2 Hz, H6), 3.33, 3.40 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.70 (3H, s, -CO2CH3), 3.79 (1H, dd, J_1 = 10.0 Hz, J_2 = 7.0 Hz, H12), 4.57, 4.78 (2x1H, ABd, J = 7.2 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.67, 4.90 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.13 (1H, br s, H17), 5.16 (1H, br s, H'17), 5.44 (1H, br s, H1)

^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0 (C2), 26.1 (C18), 26.5 (C11), 34.5 (C3), 39.1 (C14), 43.3 (C8), 43.7 (C15), 46.9 (C9), 49.2 (C4), 49.5 (C6), 51.1 (C5), 51.6 (-$CO_2\underline{C}H_3$), 54.9, 55.2 (12-$OCH_2O\underline{C}H_3$, 13-$OCH_2O\underline{C}H_3$), 77.5 (C12), 86.5 (C13), 91.2 (13-O$\underline{C}H_2OCH_3$), 96.8 (12-O$\underline{C}H_2OCH_3$), 110.1 (C17), 114.0 (C1), 140.5 (C10), 145.6 (C16), 176.4 (C7), 181.0 (C19).

MS (EI) *m/z* 450 (M^+, 19%), 405 (50), 388 (15), 373 (41), 343 (35), 328 (53), 314 (46), 297 (51), 283 (100), 269 (44), 255 (47), 239 (43), 211 (56), 129 (36), 105 (47). **HRMS** (EI) *m/z* calcd for M^+, $C_{24}H_{34}O_8$: 450.2254; found 450.2252.

Methyl *ent*-19-chloro-12α,13-di(methoxymethoxy)-19-oxo-20-norgibberella-1(10),16-dien-7-oate (177)



A vigorously stirred solution of oxalyl chloride (0.54 ml, 6.1 mmol, 12 eq) in dry ether (10 ml) containing 1 drop of DMF under an atmosphere of nitrogen was cooled to -30°C. The acid **176** (230 mg, 0.51 mmol) dissolved in dry ether (4.0 ml) and pyridine (1.5 ml) was slowly added to the oxalyl chloride solution. The solution was then left overnight to warm to room temperature. The reaction was worked up by filtering through a sintered funnel and washing the solid residue thoroughly with dry ether (5x20 ml). The solvent was removed *in vacuo* and the excess oxalyl chloride and pyridine were removed by azeotroping with dry benzene (4x30 ml). Finally, filtration through a small plug of celite followed by removal of the solvent *in vacuo* furnished the desired acid chloride **177** (197 mg, 82%) as a yellow oil.

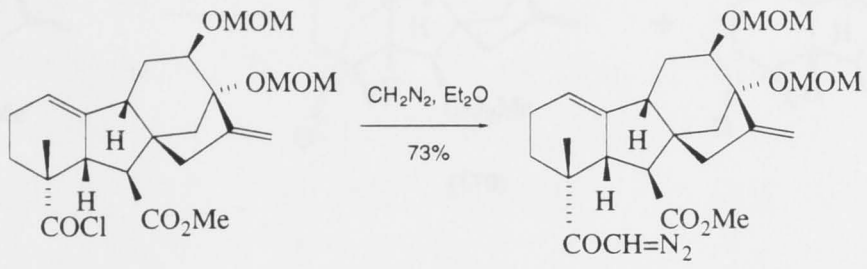
IR 1815, 1730 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (3H, s, H18), 1.20 - 2.70 (11H, m), 2.87 (1H, d, J = 6.2 Hz, H6), 2.98 (1H, br s, H5), 3.35, 3.39 (2x3H, s, $-OCH_2OC\underline{H}_3$), 3.71 (3H, s, $-CO_2CH_3$), 3.79 (1H, dd, J_1 = 10.4 Hz, J_2 = 6.7 Hz, H12), 4.59, 4.81 (2x1H, ABd, J = 6.9 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.68, 4.91 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.14 (1H, br s, H17), 5.18 (1H, br s, H'17), 5.43 (1H, br s, H1).

^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5 (C2), 25.4 (C18), 26.5 (C11), 35.6 (C3), 39.5 (C14), 44.2 (C15), 47.0 (C9), 49.5 (C8 and C6 overlapped), 51.4 (C5), 51.8 ($-CO_2\underline{C}H_3$), 54.1 (C4), 55.2, 55.3 ($13\text{-}OCH_2O\underline{C}H_3$, $12\text{-}OCH_2O\underline{C}H_3$), 77.8 (C12), 86.4 (C13), 91.5 ($13\text{-}O\underline{C}H_2OCH_3$), 97.0 ($12\text{-}O\underline{C}H_2OCH_3$), 110.4 (C17), 113.3 (C1), 140.7 (C10), 145.3 (C16), 176.0 (C7 and C19 overlapped).

MS (EI) *m/z* 468 (M^+, 6%), 423 (16), 373 (7), 344 (16), 328 (40), 297 (21), 283 (100), 269 (34), 239 (30), 211 (34). **HRMS** (EI) *m/z* calcd for M^+, $C_{24}H_{33}O_7{}^{35}Cl$: 468.1915; found 468.1914.

Methyl *ent*-12α,13-di(methoxymethoxy)-19-diazomethyl-19-oxo-20-norgibberella-1(10),16-dien-7-oate (178)



(177) (178)

The acid chloride **177** (197 mg, 0.42 mmol) in ether (10 ml) was slowly cannulated into a dried solution of diazomethane in ether (100 ml) at -30°C under an atmosphere of nitrogen. After 14 h at room temperature, TLC analysis indicated a mixture of two compounds had formed. The solvent was removed *in vacuo* and the residue was purified on silica gel (hexane/ethyl acetate, 2:1) to afford, in order of elution, the acid chloride **177** (20 mg, 10%) followed by the desired diazoketone **178** (146 mg, 73%) as a yellow oil.

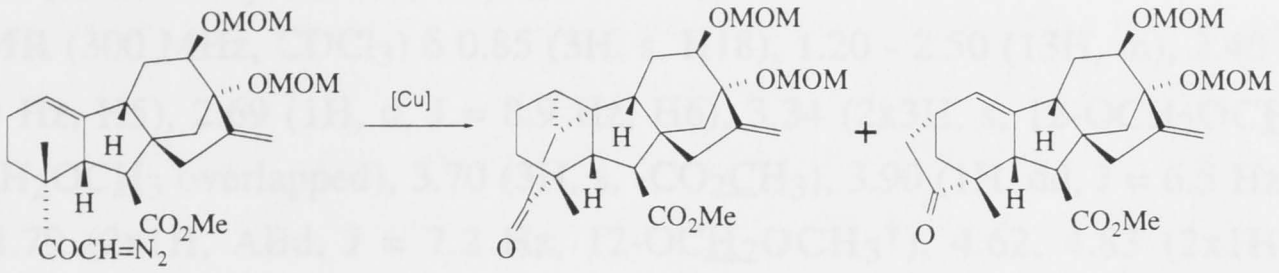
R_f : 0.71 (hexane:ethyl acetate, 1:1). **IR** 2108, 1730, 1635 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (3H, s, H18), 1.50 - 2.60 (11H, m), 2.77 (1H, br s, H5), 2.94 (1H, d, J = 5.8 Hz, H6), 3.34, 3.38 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.69 (3H, s, -CO_2CH_3), 3.82 (1H, dd, J_1 = 10.4 Hz, J_2 = 6.7 Hz, H12), 4.57, 4.79 (2x1H, ABd, J = 7.0 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.68, 4.90 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.12 (1H, br s, H17), 5.16 (1H, br s, H'17), 5.39 (1H, s, -$COCH{=}N_2$), 5.42 (1H, br s, H1).

^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1 (C2), 26.1 (C18), 26.6 (C11), 34.5 (C3), 39.4 (C14), 43.7 (C15), 46.3 (C8), 47.0 (C9), 49.1 (C4), 49.6 (C6), 51.6 (-$CO_2\underline{C}H_3$), 51.6 (C5), 53.6 (19-$CO\underline{C}H{=}N_2$), 55.2 (13-$OCH_2O\underline{C}H_3$ and 12-$OCH_2O\underline{C}H_3$ overlapped), 77.7 (C12), 86.5 (C13), 91.4 (13-$O\underline{C}H_2OCH_3$), 96.9 (12-$O\underline{C}H_2OCH_3$), 110.1 (C17), 113.4 (C1), 141.1 (C10), 145.6 (C16), 176.4 (C7), 197.2 (C19).

MS (EI) *m/z* 446 (M^+-N_2, 5%), 401 (39), 369 (31), 339 (27), 311 (22), 281 (23), 267 (24), 239 (37), 225 (26), 211 (36), 195 (23), 179 (26) 143 (32), 129 (36), 105 (47), 91 (100), 69 (43). **HRMS** (EI) *m/z* calcd for M^+, $C_{25}H_{34}O_7N_2$: 474.2366; found 474.2365.

Methyl *ent*-12α,13-di(methoxymethoxy)-19-oxo-1β,20-cyclo-19,20-cyclogibberell-16-en-7-oate (179)



(178) (179) (180)

Table 8. Results of Cyclopropanation reactions.

	^{1}H NMR yield, (Isolated yield)	
Procedure ††	**179**	**180**
A (copper-bronze)	no reaction	no reaction
B (copper(II)acetylacetonate)	25%	75%
C‡‡ (di-*t*-butylsalicyl-imidato cuprate)	75%, (53%)	25% (20%)

††General procedures from p 98

‡‡Purification of the reaction mixture on silica gel (hexane/ethyl acetate, 3:1) provided in order of elution.

Methyl *ent*-12α,13-di(methoxymethoxy)-19-oxo-2,19-methanogibberella-1(10),16-dien-7-oate (180, oil).

R_f : 0.59 (hexane:ethyl acetate, 1:1). **IR** 1735 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (3H, s, H18), 1.20 - 2.60 (11H, m), 2.52 (1H, d, J = 6.0 Hz, H6), 2.70 (1H, br s, H5), 3.10 (1H, dd, J_1 = 6 Hz, J_2 = 2.6 Hz, H2), 3.32, 3.39 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.70 (3H, s, -$CO_2C\underline{H}_3$), 3.73 (1H, m, H12), 4.50, 4.73 (2x1H, ABd, J = 6.8 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.65, 4.91 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.12 (1H, br s, H17), 5.16 (1H, br s, H'17), 5.74 (1H, m, H1).

^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2 (C18), 26.8 (C11), 30.9 (C2), 39.4 (C20), 43.7 (C3), 44.3 (C15), 46.2 (C9), 48.7 (C6), 49.1 (C14 and C8 overlapped), 50.9 (C4), 51.7 (-$CO_2\underline{C}H_3$), 54.8 (C5), 55.3 (13-$OCH_2O\underline{C}H_3$ and 12-$OCH_2O\underline{C}H_3$ overlapped), 77.5 (C12), 86.2 (C13), 91.4 (13-$O\underline{C}H_2OCH_3$), 97.0 (12-$O\underline{C}H_2OCH_3$), 110.7 (C17), 121.6 (C1), 141.6 (C10), 144.8 (C16), 175.7 (C7), 219.3 (C19).

MS (EI) *m/z* 446 (M^+, 14%), 415 (15), 401 (100), 369 (80), 339 (62), 310 (42), 267 (35), 237 (47), 211 (48), 178 (33), 145 (46), 119 (54), 105 (64), 90 (49), 56 (71).

HRMS (EI) *m/z* calcd for M^+, $C_{25}H_{34}O_7$: 446.2305; found 446.2306.

Methyl *ent*-12α,13-di(methoxymethoxy)-19-oxo-1β,20-cyclo-19,20-cyclogibberell-16-en-7-oate (**179**, white solid).

R_f : 0.50 (hexane:ethyl acetate, 1:1). **IR** 1735 cm^{-1}.

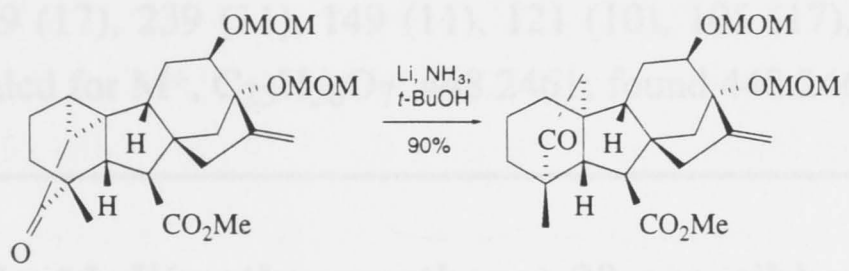
^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, s, H18), 1.20 - 2.50 (13H, m), 2.40 (1H, d, J = 8.9 Hz, H5), 2.69 (1H, d, J = 8.9 Hz, H6), 3.34 (2x3H, s, 12-$OCH_2OC\underline{H}_3$, and 13-$OCH_2OC\underline{H}_3$ overlapped), 3.70 (3H, s, -$CO_2\underline{C}H_3$), 3.90 (1H, dd, J = 6.5 Hz, H12), 4.53, 4.79 (2x1H, ABd, J = 7.2 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.62, 4.83 (2x1H, ABd, J = 6.7 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.15 (1H, br s, H17) 5.25 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 15.2 (C18), 17.3 (C2), 27.6 (C11), 30.0 (C1), 32.1 (C20), 38.1 (C3), 42.3 (C14), 43.1 (C10), 44.2 (C9), 45.4 (C15), 47.8 (C4), 50.5 (C8), 50.8 (C6 and -CO_2CH_3 overlapped), 51.7 (C5), 55.2, 55.4 (12-$OCH_2O\underline{C}H_3$, 13-$OCH_2O\underline{C}H_3$), 78.6 (C12), 86.4 (C13), 91.5 (13-$O\underline{C}H_2OCH_3$), 96.4 (12-$O\underline{C}H_2OCH_3$), 112.2 (C17), 144.8 (C16), 173.9 (C7), 213.8 (C19).

MS (EI) *m/z* 446 (M^+, 13%), 415 (15), 401 (100), 369 (46), 339 (25), 311 (23), 281 (19), 225 (19), 205 (28), 175 (39), 135 (26), 105 (29), 90 (36) 69 (31), 54 (27).

HRMS (EI) *m/z* calcd for M^+, $C_{25}H_{34}O_7$: 446.2305; found 446.2306.

Methyl *ent*-12α,13-di(methoxymethoxy)-19-oxo-19,20-cyclogibberell-16-en-7-oate (**181**)



(**179**) (**181**)

Compound **179** (26 mg, 0.058 mmol) was dissolved in dry THF (1.7 ml) containing *t*-butyl alcohol (17 µl, 0.18 mmol). After cooling to -78°C, liquid ammonia (approximately 15 ml) was distilled into the flask from a sodium amide solution. Lithium metal (approximately 1.6 mg, 0.23 mg atom) was added in small pieces with vigorous stirring . The reaction was quenched with sat. ammonium chloride solution (5 ml) upon the appearance of a deep blue colour that persisted for 5 sec. The ammonia was then allowed to evaporate under a gentle flow of nitrogen. The white solid residue was dissolved in water (10 ml) and ethyl acetate (50 ml), the layers were separated and the aqueous layer was extracted with ethyl acetate (2x10 ml). The combined organic phases were washed with brine (15 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo* to yield a yellow oil. The residue was dissolved in dichloromethane (10 ml) and treated with Dess-Martin periodinane (100 mg, 0.24 mmol, 2 eq). After

15 min TLC analysis indicated that the reaction was complete. Sat. sodium bicarbonate solution containing 7% sodium thiosulfate (20 ml) was added, and reaction mixture was left stirring until the cloudiness had dissipated. The reaction mixture was diluted with ethyl acetate (60 ml), the layers were separated and the organic phase was washed with sat. sodium bicarbonate solution (10 ml) and brine (1x10 ml). The combined aqueous phases were back-extracted with ethyl acetate (2x20 ml). The combined organic phases were dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 2:1) afforded the desired cyclopentanone **181** (23.5 mg, 90%) as a colourless oil.

R_f : 0.65 (hexane:ethyl acetate, 1:1). **IR** 1730 cm^{-1}.

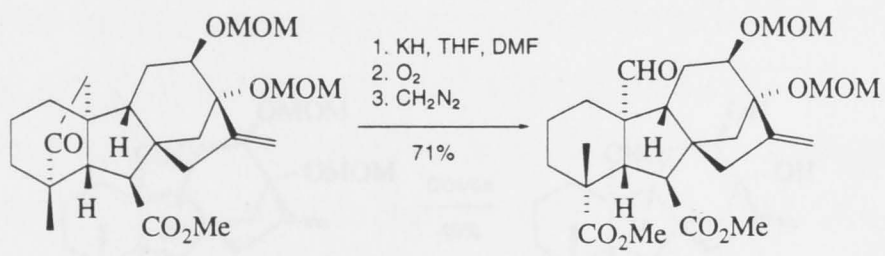
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, s, H18), 1.20 - 2.40 (15H, m), 2.40 (2H, s, H5 and H6 overlapped), 3.35, 3.38 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.69 (3H, s, -CO_2CH_3), 4.29 (1H, m, H12), 4.53, 4.78 (2x1H, ABd, J = 7.2 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.64, 4.86 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.13 (1H, br s, H17), 5.29 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9 (C18), 19.6 (C2), 28.9 (C11), 36.4 (C20), 37.9 (C1), 41.3 (C3), 43.3 (C14), 44.6 (C15), 48.5, 48.8 (C10, C4), 51.7 (C6), 51.8 (-$CO_2\underline{C}H_3$), 52.0 (C9), 53.6 (C8), 55.3 (13-$OCH_2O\underline{C}H_3$ and 12-$OCH_2O\underline{C}H_3$ overlapped), 59.7 (C5), 78.5 (C12), 87.6 (C13), 91.6 (13-$O\underline{C}H_2OCH_3$), 95.7 (12-$O\underline{C}H_2OCH_3$), 112.8 (C17), 144.8 (C16), 173.2 (C7), 219.8 (C19).

MS (EI) *m/z* 448 (M^+, 1%), 417 (12), 403 (100), 388 (13), 371 (54), 341 (29), 311 (16), 283 (11), 269 (17), 239 (11), 149 (11), 121 (10), 105 (17), 91 (254), 55 (21).

HRMS (EI) *m/z* calcd for M^+, $C_{25}H_{36}O_7$: 448.2461; found 448.2460.

Dimethyl *ent*-12α,13-di(methoxymethoxy)-20-oxo-gibberell-16-ene-7,19-dioate (182)

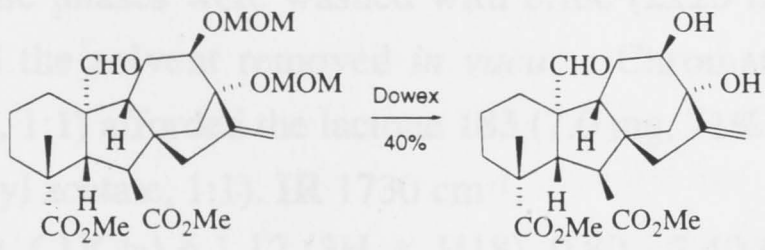


(181) (182)

An excess of dry (oil free) potassium hydride (approximately 35 mg, 33 mmol) was added to a solution of the cyclopentanone **181** (70 mg, 0.156 mmol) in dry THF (4 ml) and dry DMF (4 ml) at 0°C stirring under an atmosphere of nitrogen. The reaction mixture was left stirring for 2 h, after which time the reaction flask was thoroughly flushed with nitrogen before a steady stream of dry oxygen gas was passed through the solution. After 20 min TLC analysis indicated that the reaction was

complete. The reaction was throughly flushed with nitrogen, then carefully quenched with methanol (5 ml), and the solvent removed *in vacuo*. The DMF was removed under high vacuum with gentle heating. The solid residue was dissolved in water (20 ml) and ethyl acetate (50 ml), the layers were separated and the aqueous phase was extracted with ethyl acetate (2x20 ml). The combined organic phases were washed with brine (10 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. The residue was dissolved in methanol (10 ml) and treated with an excess of diazomethane. The solvent was removed under a gentle stream of nitrogen. Purification on silica gel (hexane/ethyl acetate, 3:1) afforded the desired aldehyde **182** (55 mg, 71%) as an oil.
R_f : 0.42 (hexane:ethyl acetate, 2:1). **IR** 1730 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (3H, s, H18), 0.90 - 2.50 (13H, m), 2.20 (1H, d, J = 12.2 Hz, H5), 3.30 (6H, s, 12-$OCH_2OC\underline{H}_3$ and 13-$OCH_2OC\underline{H}_3$ overlapped), 3.64, 3.70 (2x3H, s, -CO_2CH_3), 3.73 (1H, d, J = 12.2 Hz, H6), 3.81 (1H, m, J = 7.2 Hz, H12), 4.52, 4.81 (1H, d, J = 7.2 Hz, 13-$OC\underline{H}_2OCH_3$†), 4.62, 4.78 (1H, d, J = 6.6 Hz, 12-$OC\underline{H}_2OCH_3$†), 5.10 (1H, br s, H17), 5.16 (1H, br s, H'17), 9.67 (1H, s, H20).
^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (C2), 26.9 (C11), 27.7 (C18), 32.9 (C1), 37.4 (C3), 44.2, 44.3 (C14, C15), 44.7 (C4), 47.9 (C8), 49.5 (C6), 51.6, 51.8 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 55.3, 55.5 (13-$OCH_2O\underline{C}H_3$, 12-$OCH_2O\underline{C}H_3$), 55.6 (C9), 57.0 (C5), 59.9 (C10), 78.6 (C12), 86.0 (C13), 91.5 (13-$O\underline{C}H_2OCH_3$), 96.5 (12-$O\underline{C}H_2OCH_3$), 111.5 (C17), 144.5 (C16), 174.9, 176.2 (C19, C7), 205.1 (C20).
MS (EI) *m/z* 494 (M^+, 7%), 463 (9), 449 (49), 417 (100), 387 (95), 373 (89), 358 (74), 329 (70), 299 (70), 269 (46), 239 (55), 211 (39), 179 (35), 135 (29) 91 (27) 69 (28). **HRMS** (EI) *m/z* calcd for M^+, $C_{26}H_{38}O_9$: 494.2516; found 494.2514.

Dimethyl *ent*-12α,13-di(hydroxy)-20-oxo-gibberell-16-ene-7,19-dioate (142)



(182) (142)

Dowex resin (150 mg of wet resin) was added to a solution of the aldehyde **182** (12 mg, 0.024 mmol) in methanol (8.3 ml) and water (1.7 ml). The reaction mixture was then heated under reflux for 48 h. TLC analysis indicated that two major compounds were present. The reaction mixture was diluted with ethyl acetate (50 ml) and filtered

through a pad of celite. The filtrate was then washed with brine (10 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 1:1) afforded only the desired deprotected aldehyde **142** (4 mg, 40%).

R_f : 0.28 (hexane:ethyl acetate, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (3H, s, H18), 0.80 - 2.50 (15H, m), 2.23 (1H, d, J = 11.7 Hz, H5), 3.69 (4H, s, H6 and 7-CO_2CH_3# overlapped), 3.74 (4H, s, H12 and 19-CO_2CH_3# overlapped), 5.13 (2H, br s, H17), 9.74 (1H, s, H20).

^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7 (C2), 27.7 (C18), 28.1 (C11), 33.1 (C1), 37.5 (C3), 43.3 (C14), 44.6 (C4), 48.2 (C15), 48.7 (C8), 49.1 (C6), 51.8, 51.9 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 56.9 (C9), 57.4 (C5), 59.9 (C10), 74.2 (C12), 79.8 (C13), 109.8 (C17), 149.0 (C16), 175.2, 176.3 (C19, C7), 205.0 (C20).

MS (CI) *m/z* 406 (M^++1, 100%), 375 (72), 282 (78), 136 (15).

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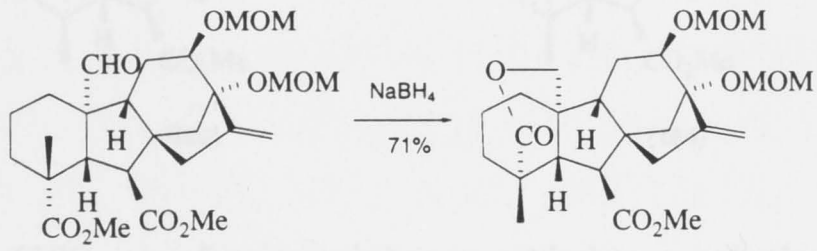
ent-20-Hydroxy-12α,13-di(methoxymethoxy)gibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (183)



(182) (183)

Sodium borohydride (3.7 mg, 0.09 mmol) was added to a solution of the aldehyde **182** (12.0 mg, 0.024 mmol) in methanol (4 ml) at 0°C. After 1 h TLC analysis indicated that the reaction was complete. The solution was diluted with ethyl actetate (50 ml) and acidified with sodium dihydrogen phosphate solution (20%, 20 ml). The layers were separated and the aqueous phase was extracted with ethyl acetate (2x10 ml). The combined organic phases were washed with brine (2x20 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 1:1) afforded the lactone **183** (7.0 mg, 71%) as an oil.

R_f : 0.39 (hexane:ethyl acetate, 1:1). **IR** 1730 cm^{-1}.

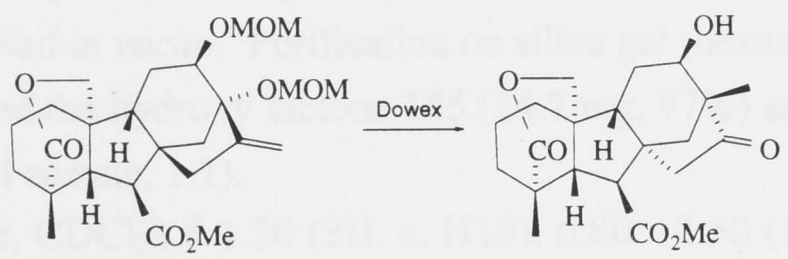
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, s, H18), 0.80 - 2.40 (13H, m), 2.24 (1H, d, J = 12.6 Hz, H5), 2.75 (1H, d, J = 12.6 Hz, H6), 3.36, 3.37 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.70 (3H, s, -CO_2CH_3), 4.07 (1H, d, J_{gem} = 12.3 Hz, 20-pro-S-H), 4.22 (1H, m, H12), 4.33 (1H, dd, J_{gem} = 12.3 Hz, $J_{20,1\beta}$ = 2.1 Hz, 20-pro-R-H), 4.52, 4.78 (2x1H, ABd, J = 7.3 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.62, 4.91 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.17 (2H, br s, H17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (C2), 23.1 (C18), 25.9 (C11), 38.3 (C1), 39.7 (C3), 41.4 (C10), 41.7 (C14), 42.6 (C4), 45.4 (C15), 47.3 (C8), 51.7 (C6), 52.0 ($-CO_2\underline{C}H_3$), 53.0, 53 (C5, C9), 55.3, 55.4 ($13\text{-}OCH_2O\underline{C}H_3$, $12\text{-}OCH_2O\underline{C}H_3$), 74.0 (C20), 78.1 (C12), 87.7 (C13), 91.7 ($13\text{-}O\underline{C}H_2OCH_3$), 96.0 ($12\text{-}O\underline{C}H_2OCH_3$), 112.8 (C17), 144.1 (C16), 173.2, 175.0 (C19, C7).

MS (EI) *m/z* 433 (M^+-OCH_3, 10%), 419 (100), 387 (32), 359 (20), 269 (18), 225 (16). **MS** (CI) *m/z* 465 (M^++1, 100%), 449 (20), 433 (55), 389 (30), 347 (26), 270 (15).

Attempted Deprotection of Compound 183

ent-12α,20-Dihydroxy-13-oxo-12(13->16)*abeo*-gibberellane-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (184)



(183) (184)

Dowex resin (100 mg of wet resin) was added to a solution of the lactone **183** (7 mg, 0.015 mmol) in methanol (6 ml) and water (1.0 ml). The reaction mixture was then heated under reflux for 48 h, after which time TLC analysis indicated that the reaction was complete. The reaction mixture was diluted with ethyl acetate (50 ml) and filtered through a pad of celite. The filtrate was then washed with brine (10 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 2:1 - 1:2) afforded the rearranged product **184** (4.2 mg 86%) as a slightly off white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (3H, s, H18), 1.14 (3H, s, H17), 0.80 - 2.40 (12H, m), 2.29 (1H, d, J = 11.5 Hz, H5), 2.52 (1H, d, J = 18.9 Hz, H14β), 2.69 (1H, d, J = 11.5 Hz, H6), 2.73 (1H, dd, J_1 = 18.9 Hz, J_2 = 4.0 Hz, H14α), 3.55 (1H, m, H12), 3.74 (3H, s, $-CO_2CH_3$), 4.10 (1H, d, J_{gem} = 12.7 Hz, 20-pro-S-H), 4.50 (1H, dd, J_{gem} = 12.7 Hz, $J_{20,1\beta}$ = 2.1 Hz, 20-pro-R-H).

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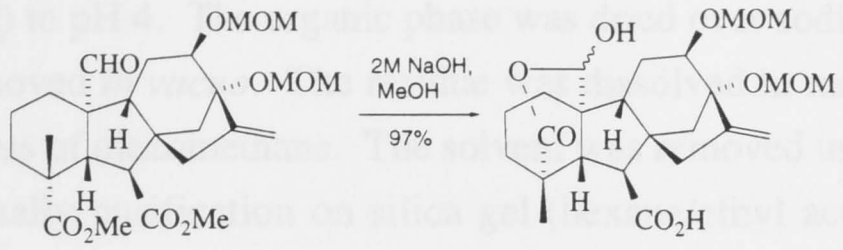
ent-20,20-Dihydroxy-12α,13-di(methoxymethoxy)gibberell-16-ene-7,19-dioic Acid 19,20-Lactone (185)



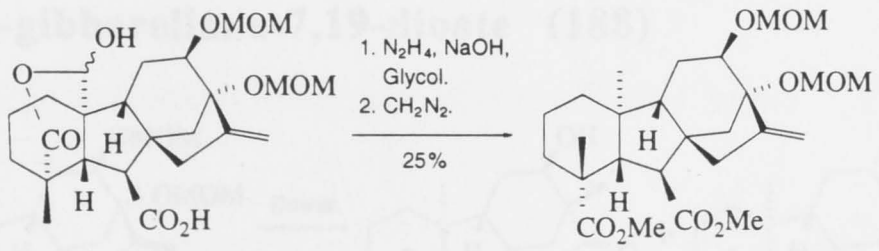
(182) (185)

The aldehyde **182** (27 mg, 0.055 mmol) was dissolved in methanol (2.0 ml) and sodium hydroxide solution (2M, 6 ml) then heated at reflux for 24 h. The mixture was diluted with ethyl acetate/20% 2-butanol (50 ml) and was acidified with phosphoric acid (10%, 10 ml). The layers were separated and the aqueous phase was extracted with the ethyl acetate/2-butanol mixture (2x20 ml). The combined organic phases were washed with brine (3x10 ml) to pH 4. The organic phase was dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Purification on silica gel (hexane/ethyl acetate/ acetic acid, 2:1:0.1) provided the hydroxy lactone **185** (24.7 mg, 97%) as a white solid.

R_f : 0.1 (hexane:ethyl acetate, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (3H, s, H18), 0.80 - 2.50 (18H, m), 2.22 (1H, d, J = 13.2 Hz, H5), 3.36 (3H, s, 13-$OCH_2OC\underline{H}_3$#), 3.38 (4H, s, 12-$OCH_2OC\underline{H}_3$# and H6 overlapped), 4.13 (1H, m, H12), 4.55, 4.80 (2x1H, ABd, J = 7.0 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.65, 4.85 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.12 (1H, br s, H17), 5.24 (1H, br s, H'17).

Dimethyl _ent_-12α,13-di(methoxymethoxy)gibberell-16-ene-7,19-dioate (186)



(185) (186)

Anhydrous hydrazine (0.25 ml) was added to a solution of the hydroxy lactone **185** (24.0 mg, 0.051 mmol) in ethylene glycol (2.0 ml) and the reaction mixture was heated at 100°C for 30 min. Half a pellet of sodium hydroxide (approximately 200 mg) was added and the temperature was rasied to 116°C for 1 h. Finally, the temperature was raised to 180°C and the reaction was left overnight. The mixture was diluted with

ethyl acetate/20% 2-butanol (50 ml) and was acidified with phosphoric acid (10%, 10 ml). The layers were separated and the aqueous phase was extracted with the ethyl acetate/2-butanol mixture (2x20 ml). The combined organic phases were washed with brine (3x10 ml) to pH 4. The organic phase was dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. The residue was dissolved in methanol (10 ml) and treated with an excess of diazomethane. The solvent was removed under a gentle stream of nitrogen, and finally purification on silica gel (hexane/ethyl acetate, 3:1) afforded compound **186** (6. mg, 25%) as a colourless oil.

R_f : 0.51 (hexane:ethyl acetate, 2:1). **IR** 1725 cm^{-1}.

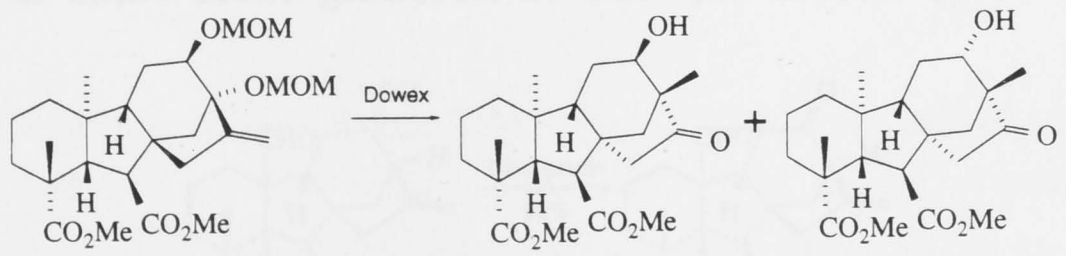
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70 (3H, s, H20), 1.04 (3H, s, H18), 0.80 - 2.30 (13H, m), 2.15 (1H, d, J = 11.4 Hz, H5), 3.35 (3H, s, 13-$OCH_2OC\underline{H}_3$#), 3.36 (4H, s, 12-$OCH_2OC\underline{H}_3$# and H6 overlapped), 3.67, 3.69 (2x3H, s, -CO_2CH_3), 3.90 (1H, m, H12), 4.55, 4.79 (2x1H, ABd, J = 7.1 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.66, 4.89 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.14 (1H, br s, H17), 5.18 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6 (C20), 19.4 (C2), 27.1 (C11), 27.9 (C18), 37.6, (C1), 38.9 (C3), 43.8, 44.2 (C4, C10), 45.1, 45.2 (C14, C15), 48.0 (C8), 50.1 (C6), 51.4, 51.6 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 55.3, 55.4 (13-$OCH_2O\underline{C}H_3$, 12-$OCH_2O\underline{C}H_3$), 56.5 (C9), 58.5 (C5), 79.7 (C12), 86.1 (C13), 91.5 (13-$O\underline{C}H_2OCH_3$), 96.7 (12-$O\underline{C}H_2OCH_3$), 111.0 (C17), 145.6 (C16), 175.8, 177.3 (C19, C7).

MS (EI) *m/z* 480 (M^+, 4%), 435 (100), 403 (33), 375 (57), 344 (39), 315 (32), 299 (50), 271 (31), 241 (32), 181 (57), 143 (63), 57 (50). **HRMS** (EI) *m/z* calcd for M^+, $C_{26}H_{40}O_8$: 480.2723; found 480.2723.

Attempted Deprotection of Compound 186

Dimethyl *ent*-12α,20Dihydroxy-13-oxo-12(13->16)*abeo*-gibberellane-7,19-dioate (187) and **Dimethyl-*ent*-12β,20Dihydroxy-13-oxo-12(13->16)*abeo*-gibberellane-7,19-dioate (188)**



(186) (187) (188)

Dowex resin (80 mg of wet resin) was added to a solution of the compound **186** (6.0 mg, 0.012 mmol) in methanol (9 ml) and water (1.6 ml). The reaction was then heated under reflux for 44 h. The reaction mixture was cooled, diluted with ethyl acetate

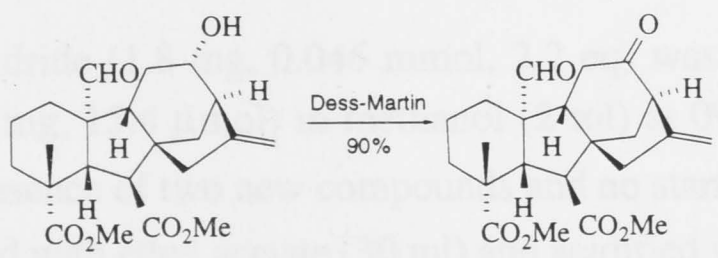
(50 ml) and filtered through a pad of celite. The filtrate was then washed with brine (10 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 1:1) afforded a mixture of the rearranged products **187** and **188** in order of elution.

Compound 12β-OH (**187**, 3.0 mg, 61%)
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.62 (3H, s, H20), 1.07 (6H, s, H18 and H17 overlapped), 0.80 - 2.30 (12H, m), 2.08 (1H, d, J = 11.6 Hz, H5), 2.30 (1H, d, J = 18.7 Hz, H14β), 2.73 (1H, dd, J_1 = 18.7 Hz, J_2 = 4.0 Hz, H14α), 3.49 (1H, d, J = 11.6 Hz, H6), 3.56 (1H, br s, H12), 3.66, 3.73 (2x3H, s, $-CO_2CH_3$).
^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2 (C17), 17.1 (C20), 19.4 (C2), 27.8 (C18), 28.3 (C11), 37.7, (C1), 38.1 (C3), 42.3 (C4), 43.5 (C13), 44.0 (C10), 47.2 (C14), 49.8 (C6), 49.9 (C15), 51.4, 51.6 ($7-CO_2\underline{C}H_3$, $19-CO_2\underline{C}H_3$), 52.8 (C9), 57.0 (C8), 59.5 (C5), 175.4, 177.2 (C19, C7), 217.5 (C16).

compound 12α-OH (**188**, 2.0 mg, 39%)
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.65 (3H, s, H20), 1.05 (3H, s, H18), 1.12 (3H, s, H17), 0.80 - 2.30 (12H, m), 2.30 (1H, d, J = 11.6 Hz, H5), 2.35 (1H, d, J = 18.9 Hz, H14β), 2.70 (1H, dd, J_1 = 18.9 Hz, J_2 = 3.8 Hz, H14α), 3.48 (1H, d, J = 11.6 Hz, H6), 3.54 (1H, br s, H12), 3.67, 3.72 (2x3H, s, $-CO_2CH_3$).
^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6 (C17), 16.2 (C20), 19.4 (C2), 27.8 (C18), 28.3 (C11), 37.7, (C1), 38.1 (C3), 42.3 (C4), 43.5 (C13), 44.0 (C10), 47.2 (C14), 49.8 (C6), 49.9 (C15), 51.4, 51.6 ($7-CO_2\underline{C}H_3$, $19-CO_2\underline{C}H_3$), 52.8 (C9), 57.0 (C8), 59.5 (C5), 175.4, 177.2 (C19, C7), 217.5 (C16).

8.5.5 12β-MONOHYDROXY SERIES

Dimethyl *ent*-12,20-dioxo-gibberell-16-ene-7,19-dioate (189)



(**136**) (**189**)

The alcohol **136** (8 mg, 0.018 mmol) was dissolved in dichloromethane (5 ml) and treated with Dess-Martin periodinane (15 mg, 0.037 mmol, 2 eq). After 15 min TLC

analysis indicated that the reaction was complete. Sat. sodium bicarbonate solution containing 7% sodium thiosulfate (20 ml) was added, and the reaction mixture was left stirring until the cloudiness had dissipated. The reaction mixture was diluted with ethyl acetate (40 ml), the layers were separated and the organic phase was washed with sat. sodium bicarbonate solution (10 ml) and brine (1x10 ml). The combined aqueous phases were back-extracted with ethyl acetate (2x20 ml). The combined organic phases were dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 3:1) afforded the desired keto aldehyde **189** (6.5 mg, 90%) as a colourless oil.

R_f : 0.8 (hexane:ethyl acetate, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.156 (3H, s, H18), 0.90 - 2.50 (13H, m), 2.36 (1H, d, J = 12.9 Hz, H5), 3.23 (1H, d, J = 5.0 Hz, H13), 3.63, 3.76 (2x3H, s, -CO_2CH_3), 4.02 (1H, d, J = 12.9 Hz, H6), 5.07 (1H, br s, H17), 5.17 (1H, br s, H'17), 9.72 (1H, s, H20).

^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (C2), 27.8 (C18), 32.8 (C1), 35.6, 36.8, 37.5 (CH_2, CH_2, CH_2), 45.3 (C4), 46.3 (C15), 49.2 (C8), 49.6 (C13), 51.7, 51.9 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 52.4 (C6), 55.9 (C9), 57.0 (C5), 60.1 (C10), 112.4 (C17), 143.3 (C16), 174.3, 176.4 (C19, C7), 205.0 (C20), 206.3 (C12).

MS (EI) *m/z* 386 (M^+ - H_2, 5%), 356 (16), 328 (56), 300 (100), 269 (25), 256 (15), 239 (39), 225 (15), 209 (21), 197 (48), 181 (19), 149 (26), 119 (38), 91 (37), 79 (26).

HRMS (EI) *m/z* calcd for M^+ - H_2, $C_{22}H_{26}O_6$: 386.1729; found 386.1730.

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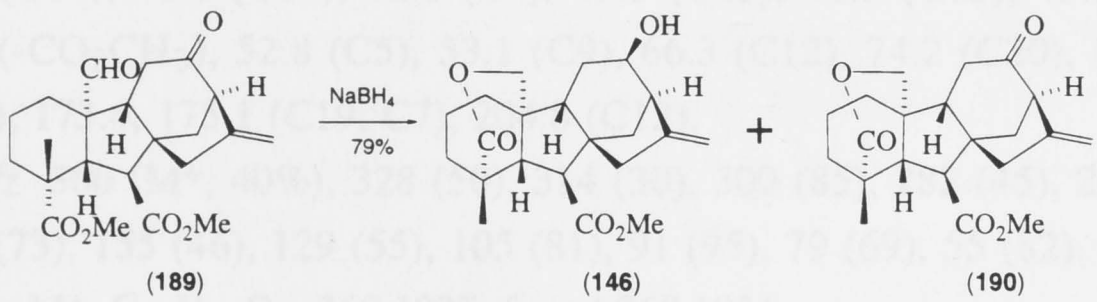
ent-12α,20-Dihydroxygibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (146)



(189) (146) (190)

Sodium borohydride (1.8 mg, 0.046 mmol, 2.2 eq) was added to a solution of the aldehyde **189** (6.0 mg, 15.4 μmol) in methanol (2 ml) at 0°C. After 30 min TLC analysis showed the presence of two new compounds and no starting material remaining. The solution was diluted with ethyl acetate (30 ml) and acidified with sodium dihydrogen phosphate solution (20%, 10 ml). The layers were separated and the aqueous phase was extracted with ethyl acetate (2x10 ml). The combined organic phases were washed with brine (2x10 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 3:1) afforded in order of elution:

***ent*-20-Hydroxy-12-oxo-gibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone** (**190**, 2.3 mg, 39%)

R_f : 0.64 (hexane:ethyl acetate, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (3H, s, H18), 0.50 - 2.50 (13H, m), 2.09 (1H, d, J = 12.6 Hz, H5), 2.63 (1H, d, J = 12.6 Hz, H6), 3.11 (1H, d, J = 4.8 Hz, H13), 3.30 (3H, s, $-CO_2CH_3$), 3.43 (1H, d, J = 12.0 Hz, H20), 3.83 (1H, d, J = 12.0 Hz, H'20), 5.00 (1H, s, H17), 5.36 (1H, s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0 (C2), 24.1 (C18), 34.9 (C11), 37.5 (C1), 38.2 (C3), 40.0 (C14), 41.6 (C10), 43.0 (C4), 47.1 (C15), 49.7 (C8), 51.6 (C13), 51.7 ($-CO_2\underline{C}H_3$), 51.8 (C6), 54.4 (C5), 56.6 (C9), 73.4 (C20), 112.5 (C17), 144.6 (C16), 173.3 (C19 and C7 overlapped), 204.8 (C12).

MS (EI) *m/z* 358 (M^+, 70%), 328 (43), 312 (33), 298 (63), 253 (100), 225 (35), 211 (40), 197 (62), 129 (50), 105 (70), 91 (77), 79 (57), 55 (70). **HRMS** (EI) *m/z* calcd for M^+, $C_{21}H_{26}O_5$: 358.1780; found 358.1780.

***ent*-12α,20-Dihydroxygibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone** (**146**, 2.4 mg, 40%)

R_f : 0.26 (hexane:ethyl acetate, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (3H, s, H18), 1.20 - 2.30 (14H, m), 2.30 (1H, d, J = 12.7 Hz, H5), 2.77 (1H, d, J = 12.7 Hz, H6), 2.92 (1H, m, H13), 3.70 (3H, s, $-CO_2CH_3$), 4.07 (1H, d, J_{gem} = 12.1 Hz, 20-pro-S-H), 4.19 (1H, m, H12), 4.34 (1H, dd, J_{gem} = 12.1 Hz, $J_{20,1\beta}$ = 2.4 Hz, 20-pro-R-H), 5.11 (1H, s, H17), 5.21 (1H, s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (C2), 23.3 (C18), 27.8 (C11), 37.6 (C1), 38.3 (C3), 39.8 (C14), 41.6 (C10), 42.6 (C4), 45.9 (C13), 46.3 (C15), 49.9 (C8), 51.7 (C6), 52.0 ($-CO_2\underline{C}H_3$), 52.8 (C5), 53.1 (C9), 66.3 (C12), 74.2 (C20), 112.5 (C17), 147.3 (C16), 173.4, 175.1 (C19, C7), 204.8 (C12).

MS (EI) *m/z* 360 (M^+, 40%), 328 (50), 314 (30), 300 (85), 282 (45), 255 (90), 237 (100), 211 (73), 155 (46), 129 (55), 105 (81), 91 (95), 79 (69), 55 (82). **HRMS** (EI) *m/z* calcd for M^+, $C_{21}H_{28}O_5$: 360.1937; found 360.1936.

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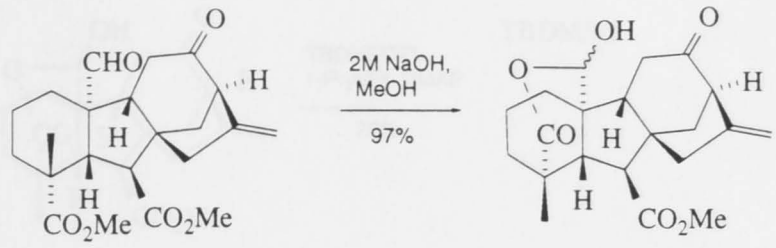
ent-20,20-Dihydroxy-12-oxogibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (191)



(189) (191)

The aldehyde **189** (25 mg, 0.064 mmol) was dissolved in methanol (2.5 ml), THF (3 ml), and sodium hydroxide solution (2M, 7.5 ml) and reaction left stirring for 15 min. The mixture was diluted with ethyl acetate (50 ml) and was acidified with phosphoric acid (10%, 10 ml). The layers were separated and the aqueous phase was extracted with the ethyl acetate (2x20 ml). The combined organic phases were washed with brine (3x10 ml) to pH 4, dried over sodium sulfate, filtered, and the solvent removed *in vacuo* to provide the monoester **191** (23.9 mg, 97%) as a white solid. The material was used immediately without further purification.

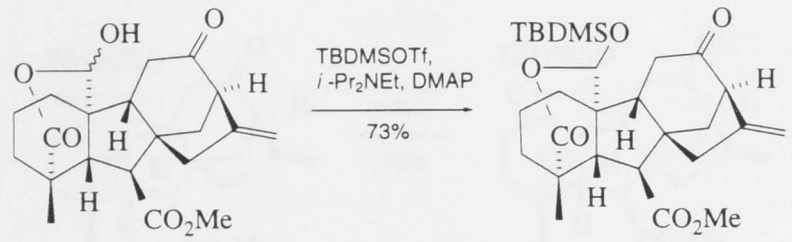
R_f : 0.12 (hexane:ethyl acetate, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (3H, s, H18), 0.80 - 2.60 (14H, m), 2.36 (1H, d, J = 13.2 Hz, H5), 3.02 (1H, d, J = 13.2 Hz, H6), 3.25 (1H, br s, H13), 3.72 (3H, s, -CO_2CH_3), 5.08 (1H, br s, H17), 5.19 (1H, br s, H'17), 6.0 (1H, broad unresolved singlet, H20).

^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (C2), 23.3 (C18), 29.6 (C1), 36.5 (C1 and C3 overlapped), 39.8 (C14), 42.9 (C4), 46.6 (C15), 49.4 (C8 and C10 overlapped), 50.5 (C13), 51.4 (7-$CO_2\underline{C}H_3$), 52.1 (C6), 54.8 (C9), 55.9 (C5), (C20 not observed), 112.8 (C17), 143.0 (C16), 173.3, 175.8 (C19, C7), 208.1 (C12).

MS (EI) *m/z* 374 (M^+, 13%), 356 (30), 342 (97), 314 (83), 300 (58), 269 (57), 257 (35), 239 (78), 223 (37), 211 (45), 197 (87), 157 (47), 131 (75), 119 (78), 105 (93), 91 (100), 79 (60). **HRMS** (EI) *m/z* calcd for M^+ - H_2O, $C_{21}H_{24}O_5$: 356.1624; found 356.1624.

ent-20-Hydroxy-20-(*t*-butyldimethylsilyl)oxy-12-oxogibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (192)



(**191**) (**192**)

DIPEA (0.145 ml, 0.83 mmol, 12 eq), a catalytic amount of DMAP, followed by TBDMSOTf (96 µl, 0.42 mmol, 6 eq) were added to a solution of compound **191** (24 mg, 0.064 mmol) in dry dichloromethane (5 ml) at 0°C under an atmosphere of nitrogen. The reaction mixture was left to warm to room temperature. After 2 hr TLC analysis indicated the reaction was complete. Sat. sodium bicarbonate solution (2 ml) was added and the reaction was left stirring for 5 min. The solution was diluted with ethyl acetate (30 ml), layers were separated and the aqueous phase was back extracted with ethyl acetate (2x10 ml). The combined organic phases were washed with brine (1x10ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate 5:1 - 1:1) afforded the desired protected ketone **192** (23 mg, 73%) as a colourless oil.

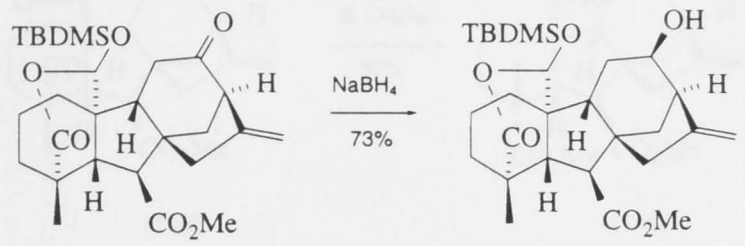
R_f : 0.85 (hexane:ethyl acetate, 1:1). **IR** 1730 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.17, 0.24 (2x3H, s, -$Si(CH_3)_2$-), 0.90 (9H, s, -$SiC(CH_3)_3$), 1.13 (3H, s, H18), 0.90 - 2.50 (13H, m), 2.34 (1H, d, J = 13.1 Hz, H5), 2.86 (1H, d, J = 13.1 Hz, H6), 3.25 (1H, d, J = 4.5 Hz, H13), 3.71 (3H, s, -CO_2CH_3), 5.07 (1H, br s, H17), 5.20 (1H, br s, H'17), 5.63 (1H, s, H20).

^{13}C NMR (75 MHz, $CDCl_3$) δ -5.60, -3.40 (-$Si(CH_3)_2$-), 17.7 (-Si$\underline{C}(CH_3)_3$), 20.7 (C2), 23.2 (C18), 25.6 (-SiC($\underline{C}H_3)_3$), 32.5 (C1), 36.6, 37.2 (C3, C11), 39.9 (C14), 42.5 (C4), 46.5 (C15), 47.5 (C8), 49.4 (C10), 50.6, 51.3 (C13, C6), 52.1 (7-$CO_2\underline{C}H_3$), 54.6 (C9), 56.0 (C5), 98.8 (C20), 112.8 (C17), 142.9 (C16), 173.0, 173.7 (C19, C7), 206.7 (C12).

MS (EI) *m/z* 431 (M^+ - $C(CH_3)_3$, 100%), 403 (22), 387 (60), 343 (16), 300 (16), 251 (40), 240 (22), 129 (28), 97 (22), 83 (26), 71 (32), 57 (42). **HRMS** (EI) *m/z* calcd for M^+ - $C(CH_3)_3$, $C_{23}H_{31}O_6Si$: 431.1890; found 431.1888.

ent-12α,20-Dihydroxy-20-_t_-butyldimethylsilyloxygibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (193)



(**192**) (**193**)

Sodium borohydride (1.1 mg, 29 μmol, 2 eq) was added to a solution of the aldehyde **192** (7 mg, 14.3 μmol) in methanol (3 ml) at 0°C. After 15 min TLC analysis showed the reaction was complete. The solution was diluted with ethyl acetate (30 ml) and acidified with sodium dihydrogen phosphate solution (20%, 10 ml). The layers were separated and the aqueous phase was extracted with ethyl acetate (2x10 ml). The combined organic phases were washed with brine (2x10 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 3:1) afforded the desired alcohol **193** (5 mg, 73%) as a colourless oil.

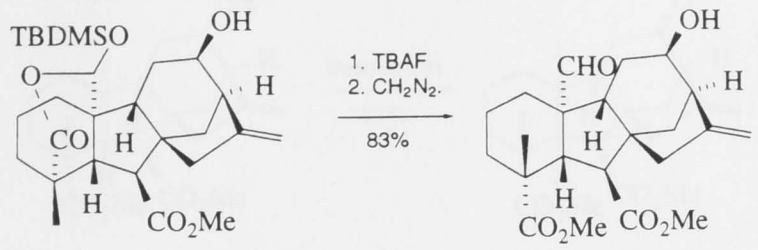
R_f : 0.85 (hexane:ethyl acetate, 1:1). **IR** 1730 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.18, 0.23 (2x3H, s, -$Si(CH_3)_2$-), 0.91 (9H, s, -$SiC(CH_3)_3$), 1.11 (3H, s, H18), 0.80 - 2.50 (14H, m), 2.20 (1H, d, J = 13.1 Hz, H5), 2.76 (1H, d, J = 13.1 Hz, H6), 2.91 (1H, m, H13), 3.69 (3H, s, -CO_2CH_3), 4.11 (1H, m, H12), 5.11 (1H, br s, H17), 5.20 (1H, br s, H'17), 5.49 (1H, s, H20).

^{13}C NMR (75 MHz, $CDCl_3$) δ -5.60, -3.40 (-$Si(CH_3)_2$-), 17.8 (-$Si\underline{C}(CH_3)_3$), 20.8 (C2), 23.4 (C18), 25.9 (-$SiC(\underline{C}H_3)_3$), 30.0 (C11), 32.7 (C1), 37.3 (C3), 40.2 (C14), 42.4 (C4), 45.9 (C13), 46.5 (C15), 47.3 (C8), 50.0 (C10), 51.0 (C6), 51.9 (7-$CO_2\underline{C}H_3$), 52.8 (C9), 54.1 (C5), 66.3 (C12), 99.4 (C20), 112.3 (C17), 147.4 (C16), 173.4, 174.2 (C19, C7).

MS (EI) *m/z* 490 (M^+, 8%), 459 (6), 433 (23), 401 (63), 345 (11), 313 (31), 283 (36), 253 (44), 225 (20), 198 (34), 180 (47), 143 (32), 105 (34), 91 (100), 73 (92). **HRMS** (EI) *m/z* calcd for M^+, $C_{27}H_{42}O_6Si$: 490.2751; found 490.2751.

Dimethyl *ent*-12α-hydroxy-20-oxo-gibberell-16-ene-7,19-dioate (145)



(193) (145)

To a solution of the alcohol **193** (6 mg, 12 µmol) in THF and water (3.7 ml, 0.122 mmol, 10 eq) was added TBAF (1M, 42 ml, 24 µmol, 2eq). After 15 min TLC indicated that the reaction was complete. The mixture was diluted with ethyl acetate (50 ml) and was acidified with sodium dihydrogen phosphate (20%, 10 ml). The layers were separated and the aqueous phase was extracted with ethyl acetate (2x20 ml). The combined organic phases were washed with brine (2x10 ml) to pH 4. The organic phase was dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. The residue was dissolved in methanol (10 ml) and treated with an excess of diazomethane, after 10 min the solvent was removed under a gentle stream of nitrogen, and finally purification on silica gel (hexane/ethyl acetate, 1:1) afforded compound **145** (4.0 mg, 83%) as a white solid.

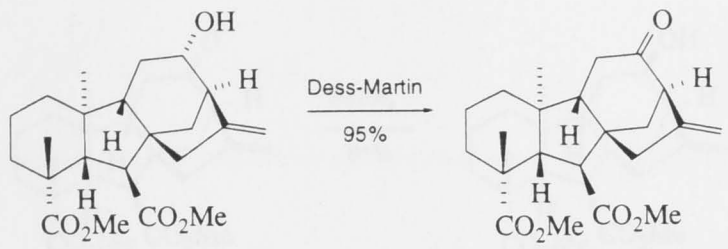
R_f : 0.20 (hexane:ethyl acetate, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, s, H18), 0.80 - 2.50 (14H, m), 2.24 (1H, d, J = 12.1 Hz, H5), 2.70 (1H, m, H13), 3.67 (3H, s, 7-CO_2CH_3#), 3.73 (4H, m, 19-CO_2CH_3# and H12 overlapped), 3.74 (1H, d, J = 12.1 Hz, H6), 5.04 (1H, br s, H17), 5.08 (1H, br s, H'17), 9.70 (1H, s, H20).

^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7 (C2), 27.9 (C18), 28.4 (C11), 33.0 (C1), 37.6 (C3), 40.7 (C14), 44.8 (C4), 45.0 (C15), 47.1 (C13), 49.3 (C6), 50.3 (C8), 51.7, 51.8 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 56.0 (C9), 57.1 (C5), 59.9 (C10), 69.3 (C12), 110.0 (C17), 147.9 (C16), 175.3, 176.4 (C19, C7), 205.3 (C20).

MS (EI) *m/z* 358 (M^+ - CH_3OH, 6%), 346 (6), 327 (77), 312 (9), 301 (10), 284 (9), 243 (11), 223 (12), 199 (85), 169 (33), 155 (57), 126 (78), 105 (35), 91 (96), 73 (52), 55 (100). **HRMS** (EI) *m/z* calcd for M^+ - CH_3OH, $C_{21}H_{26}O_5$: 358.1780; found 358.1780.

Dimethyl *ent*-12-oxo-gibberell-16-ene-7,19-dioate (194)



(**141**) (**194**)

The alcohol **141** (13.7 mg, 0.036 mmol) was dissolved in dichloromethane (5 ml) and treated with Dess-Martin periodinane[60] (30 mg, 0.074 mmol, 2 eq). After 15 min TLC analysis indicated that the reaction was complete. Sat. sodium bicarbonate solution containing 7% sodium thiosulfate (20 ml) was added, and reaction mixture was left stirring until the cloudiness had dissipated. The reaction mixture was diluted with ethyl acetate (40 ml), the layers were separated and the organic phase was washed with sat. sodium bicarbonate solution (10 ml) and brine (1x10 ml). The combined aqueous phases were back-extracted with ethyl acetate (2x20 ml). The combined organic phases were dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 3:1) afforded the desired ketone **194** (12.8 mg, 95%) as a colourless oil.

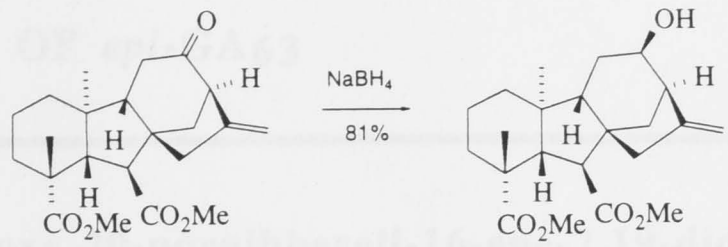
R_f : 0.40 (hexane:ethyl acetate, 3:1). **IR** 1720, 1710 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70 (3H, s, H20), 1.11 (3H, s, H18), 0.80 - 2.40 (13H, m), 2.03 (1H, d, J = 12.7 Hz, H5), 3.11 (1H, d, J = 4.4 Hz, H13), 3.46 (1H, d, J = 12.7 Hz, H6), 3.68, 3.72 (2x3H, s, $-CO_2CH_3$), 5.03 (1H, br s, H17), 5.14 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4 (C20), 19.5 (C2), 29.1 (C18), 35.5 (C11), 37.4, 37.5 (C1,C3), 39.4 (C14), 44.1, 44.5 (C4, C10), 46.4 (C15), 48.6 (C8), 50.6 (C13), 51.6 ($7\text{-}CO_2\underline{C}H_3$ and $19\text{-}CO_2\underline{C}H_3$ overlapped), 53.2 (C6), 56.6 (C9), 57.3 (C5), 111.7 (C17), 144.4 (C16), 175.0, 177.4 (C19, C7), 208.8 (C12).

MS (EI) *m/z* 374 (M^+, 9%), 342 (24), 314 (100), 299 (32), 286 (19), 255 (35), 239 (20), 211 (25), 157 (15), 107 (26), 91 (26), 79 (18), 55 (56). **HRMS** (EI) *m/z* calcd for M^+, $C_{22}H_{30}O_5$: 374.2093; found 374.2093.

Dimethyl *ent*-12α-hydroxygibberell-16-ene-7,19-dioate (147)



(194) (147)

Sodium borohydride (5.0 mg, an excess) was added to a solution of the ketone **194** (11.0 mg, 0.029 mmol) in methanol (5 ml) at 0°C. After 10 min TLC analysis showed that the reaction was complete. The solution was diluted with ethyl acetate (50 ml) and acidified with sodium dihydrogen phosphate solution (20%, 20 ml). The layers were separated and the aqueous phase was extracted with ethyl acetate (2x10 ml). The combined organic phases were washed with brine (2x20 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/ethyl acetate, 3:1) afforded the lactone **147** (9.0 mg, 81%) as an off white solid.

R_f : 0.31 (hexane:ethyl acetate, 3:1). **IR** 1725 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.68 (3H, s, H20), 1.05 (3H, s, H18), 0.80 - 2.30 (14H, m), 1.94 (1H, d, J = 12.0 Hz, H5), 2.67 (1H, t, J = 5.0 Hz, H13), 3.37 (1H, d, J = 12.0 Hz, H6), 3.67, 3.69 (2x3H, s, -CO_2CH_3), 3.81 (1H, br m, H12), 5.01 (1H, s, H17), 5.04 (1H, s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7 (C20), 19.5 (C2), 28.1 (C18), 28.6 (C11), 37.7 (C1), 39.1 (C3), 41.3 (C14), 43.7, 44.2 (C4, C10), 45.8 (C15), 47.5 (C13), 49.9 (C6), 50.2 (C8), 51.4, 51.5 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 56.9 (C9), 58.5 (C5), 70.9 (C12), 109.0 (C17), 149.1 (C16), 176.0, 177.4 (C19, C7).

MS (EI) *m/z* 376 (M^+, 2%), 344 (55), 316 (100), 301 (24), 272 (20), 257 (23), 239 (13), 213 (27), 197 (16), 181 (32), 121 (24), 107 (39), 91 (36), 79 (27), 55 (30).

HRMS (EI) *m/z* calcd for M^+, $C_{22}H_{32}O_5$: 376.2250; found 376.2251.

8.6 CHAPTER 6 EXPERIMENTAL

8.6.1 SYNTHESIS OF *epi*-GA63

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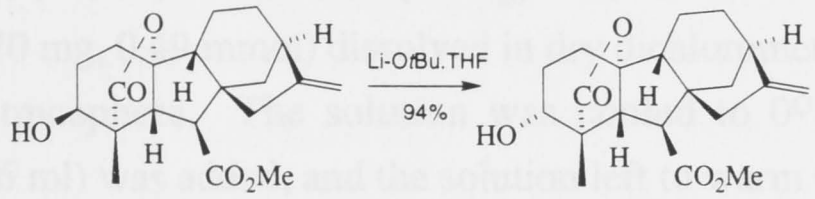
ent-3β,10β-Dihydroxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (199)



(197) (199)

A solution of lithium *t*-butoxide was formed by the addition of *n*-butyllithium (1.6 M, 2.0 ml) to dry *t*-butyl alcohol (4.5 ml) dissolved in dry THF (15 ml) with stirring at -10°C under a nitrogen atmosphere. To this solution was added GA_4-methyl ester **197** (180 mg, 0.52 mmol) dissolved in dry THF (2 ml). The solution was left to warm slowly, and was then heated at 30°C for 48 h. After this time, the solvent was removed and the residue was taken up into ethyl acetate (50 ml) and washed with saturated ammonium chloride solution (20 ml). The aqueous phase was back extracted with ethyl acetate (2x20 ml). The combined organic phases were dried over sodium sulfate, filtered and the solvent was removed *in vacuo* to yield a semi-crystalline yellow solid **199** (170mg, 94%). This material was used without further purification.

R_f : 0.16 (ethyl acetate:hexane, 1:1). **IR** 3500, 1770, 1730 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (3H, s, H18), 1.20 - 2.30 (14H, m), 2.55 (1H, d, J = 10.4 Hz, H6), 2.62 (1H, br t, H13), 2.77 (1H, m, J = 10.4 Hz, H5), 3.70 (1H, m, H3), 3.72 (3H, s, $-CO_2CH_3$), 4.84 (1H, br s, H17), 4.97 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 12.7 (C18), 16.0 (C11), 29.2, 30.0 (C1, C2), 31.2 (C12), 36.7 (C14), 38.6 (C13), 44.4 (C15), 51.3 (C5), 52.0 ($-CO_2\underline{C}H_3$), 52.3 (C8), 53.2 (C6), 54.3 (C4), 56.5 (C9), 72.7 (C3), 92.9 (C10), 107.3 (C17), 156.4 (C16), 173.0 (C19), 177.6 (C7).

MS (EI) *m/z* 346 (M^+, 1%), 286 (10), 183 (5), 169 (10), 155 (13), 143 (20), 129 (25). 115 (25), 105 (35), 91 (100).

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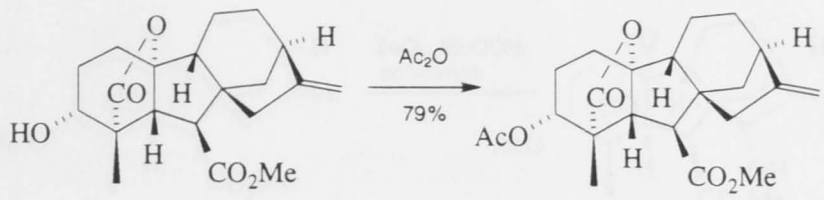
ent-3β-Acetoxy-10β-hydroxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (200)



(199) (200)

Triethylamine (1.2 ml), and DMAP (10 mg) were added to a sample of 3-*epi*-GA_4 methyl ester **199** (170 mg, 0.49 mmol) dissolved in dry dichloromethane (12 ml) stirring under a nitrogen atmosphere. The solution was cooled to 0°C with an ice bath, acetic anhydride (0.6 ml) was added, and the solution left to warm to room temperature. After 12 h the solvent was removed *in vacuo*, the residue taken up with ethyl acetate (50 ml) and the washed with sodium dihydrogen phosphate (20%, 3x10 ml), followed by brine (10 ml). The aqueous phase was extracted with ethyl acetate (2x10 ml), the combined organic layers were dried over sodium sulfate, filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (hexane/ethyl acetate, 3:1) afforded a white crystalline solid **200** (152 mg, 79%).

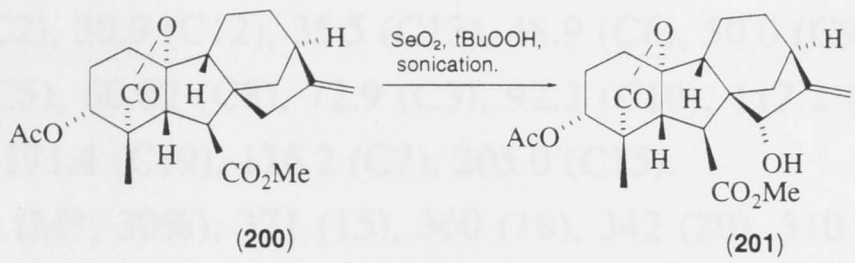
R_f: 0.56 (ethyl acetate:hexane, 1:2). **IR** 1770, 1730 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (3H, s, H18), 1.20 - 2.30 (13H, m), 2.09 (3H, s, $-COCH_3$), 2.63 (1H, t, H13), 2.65 (1H, d, J = 10.4 Hz, H6), 2.76 (1H, d, J = 10.4 Hz, H5), 3.71 (3H, s, $-CO_2CH_3$), 4.85 (1H, br s, H17), 4.90 (1H, br s, H3), 4.97 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6 (C18), 16.0 (C11), 20.8 ($-COC\underline{H}_3$), 25.7 (C1), 29.6 (C2), 31.2 (C12), 36.7 (C14), 38.6 (C13), 44.4 (C15), 51.3 (C5), 52.0 ($-CO_2\underline{C}H_3$), 52.2 (C8 and C4 overlapped), 53.2 (C6), 56.5 (C9), 73.0 (C3), 92.3 (C10), 107.5 (C17), 156.3 (C16), 170.3 ($-\underline{C}OCH_3$), 172.6 (C19), 176.3 (C7).

MS (EI) *m/z* 388 (M^+, 1%), 356 (20), 328 (20), 284 (18), 225 (20), 129 (20), 105 (30), 85 (45). **HRMS** (EI) *m/z* calcd for M^+, $C_{22}H_{28}O_6$: 388.1886; found 388.1887.

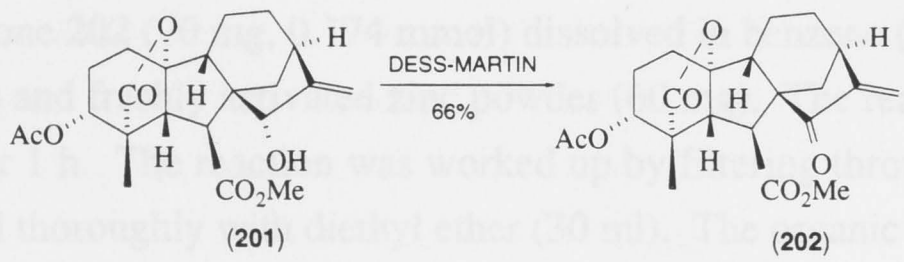
ent-3β-Acetoxy-10β,15β-dihydroxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (201)



Selenium dioxide (100 mg, 0.889 mmol, 3eq.), followed by one drop of *t*-butylhydroperoxide solution was added to a solution of the acetate **200** (115 mg, 0.294 mmol) dissolved in dry dichloromethane (2.5 ml). The mixture was sonicated for 3 h, after which time the solution was diluted with ethyl acetate (30 ml) and washed with dilute hydrochloric acid (10 ml) and water (10 ml). The combined aqueous phases were extracted with ethyl acetate (2x10 ml). The combined organic phases were washed with sodium bicarbonate (1x 10 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. The yellow residue **201** was used immediately in the next step.

R_f : 0.23 (hexane/ethyl acetate, 2:1).

ent-3β-Acetoxy-10β-hydroxy-15-oxo-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (202)



The 15α-hydroxy compound **201** was dissolved in dry dichloromethane (5 ml) and Dess-Martin[60] reagent (280 mg, 0.66 mmol, 2.0 eq.) was added. After 10 min the reaction mixture appeared as a cloudy white solution. The reaction mixture was diluted with dichloromethane (20 ml), and saturated sodium bicarbonate containing 7% sodium thiosulfate (20 ml) was added. The solution was left stirring for 20 min, the layers were separated and the organic phase was washed with saturated sodium bicarbonate (2x10 ml), and brine (15 ml), dried over sodium sulfate, filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (hexane/ethyl acetate, 2:1) yielded the desired enone **202** (68 mg, 66%, from the starting material **200**) as a white foam.

R_f : 0.32 (ethyl acetate:hexane, 1:2). **IR** 1770, 1735 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, s, H18), 1.20 - 2.35 (11H, m), 2.09 (3H, s, -COC<u>H</u>$_3$), 2.66 (1H, d, J = 10.3 Hz, H6), 2.79 (1H, d, J = 10.3 Hz, H5), 3.04 (1H,

m, H13), 3.62 (3H, s, -CO_2CH_3), 4.97 (1H, m, H3), 5.37 (1H, s, H17), 5.93 (1H, s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9 (C18), 16.5 (C11), 20.8 (-CO$\underline{C}H_3$), 25.5 (C1), 28.8, 29.1 (C14, C2), 30.9 (C12), 35.5 (C13), 48.9 (C6), 50.0 (C9), 51.9 (-$CO_2\underline{C}H_3$), 52.9 (C4), 55.5 (C5), 60.02 (C8), 72.9 (C3), 92.2 (C10), 117.2 (C17), 151.0 (C16), 170.2 (-$\underline{C}OCH_3$), 171.4 (C19), 176.2 (C7), 205.0 (C15).

MS (EI) *m/z* 402 (M^+, 30%), 371 (15), 360 (18), 342 (20), 310 (25), 282 (25), 264 (23), 238 (82), 211 (22), 183 (40), 155 (30), 143 (30), 129 (40). 117 (30), 105 (50), 91 (95), 82 (90), 55 (100). **HRMS** (EI) *m/z* calcd for M^+, $C_{22}H_{26}O_7$: 402.1679; found 402.1678.

Micro Analysis: $C_{22}H_{26}O_7.H_2O$ requires C 62.85, H 6.71; found C 62.50, H 6.74.

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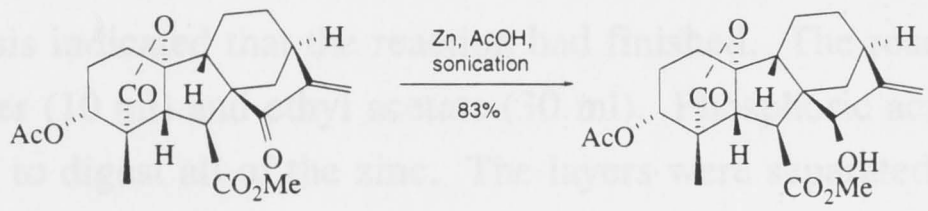
ent-3β-Acetoxy-10β,15α-dihydroxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (203)



(202) (203)

To the enone **202** (70 mg, 0.174 mmol) dissolved in benzene (2.0 ml) was added acetic acid (1 ml) and freshly activated zinc powder (60 mg). The reaction mixture was then sonicated for 1 h. The reaction was worked up by filtering through a small pad of celite and washed thoroughly with diethyl ether (30 ml). The organic phase was washed with water (10 ml), with saturated sodium bicarbonate solution (10 ml), and brine (10 ml). The organic phase was dried over sodium sulfate, filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (hexane/ethyl acetate, 2:1) yielded the desired 15β-hydroxy compound **203** (58.4 mg, 83%) as a glassy solid.

R_f: 0.61 (ethyl acetate:hexane, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (3H, s, H18), 0.80 - 2.25 (11H, m), 2.08 (3H, s, 3H, -COC$\underline{H}_3$), 2.47 (1H, dd, J_1 = 12.7 Hz, J_2 = 6.0 Hz, H9), 2.58 (1H, d, J = 10.8 Hz, H6), 2.62 (1H, t, J = 8Hz, H13), 2.79 (1H, m, J = 10.8 Hz, H5), 3.76 (3H, s, -CO_2CH_3), 3.93 (1H, br s, H15), 4.91 (1H, dd, J_1 = 10.6 Hz, J_2 = 5.8 Hz, H3), 5.10 (2H, br s, H17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5 (C18), 15.6 (C11), 20.9 (-CO$\underline{C}H_3$), 25.7 (C1), 29.1 (C2), 31.2 (C12), 31.9 (C14), 36.6 (C13), 43.0 (C6), 51.1 (C9), 52.4 (C4), 52.6 (-$CO_2\underline{C}H_3$), 55.6 (C8), 58.1 (C5), 72.9 (C3), 77.7 (C15), 92.9 (C10), 109.2 (C17), 157.0 (C16), 170.4 (-$\underline{C}OCH_3$), 174.6, 176.2 (C19, C7).

MS (EI) *m/z* 404 (M^+, 1%), 240 (10), 183 (10), 157 (15), 149 (10), 143 (15), 129 (20). 105 (25), 91 (50), 79 (30), 77 (30), 69 (30), 67 (30), 57 (55), 55 (100).
HRMS (EI) *m/z* calcd for M^+- 32, $C_{21}H_{24}O_6$: 372.1573; found 372.1575.

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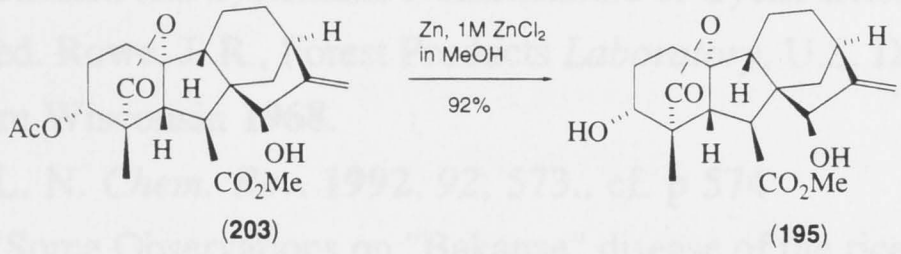
ent-3β,10β,15α-Trihydroxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (195)



(203) (195)

Freshly activated zinc (195 mg), followed by 1M zinc chloride in methanol (1.5 ml) was added to a solution of the 15β-hydroxy compound **203** (55 mg, 0.136 mmol) dissolved in methanol (6 ml). The solution was left to reflux for 4 hours, until TLC analysis indicated that the reaction had finished. The reaction was cooled, diluted with water (10 ml) and ethyl acetate (30 ml). Phosphoric acid solution (10%, 2 ml) was added to digest all of the zinc. The layers were separated and the aqueous phase was extracted with ethyl acetate (4x10 ml). The combined organic phases were washed with brine (2x15 ml), dried over sodium sulfate, filtered and the solvent removed *in vacuo* . Purification on silica gel (hexane/ethyl acetate, 3:1-1:1) yielded the desired compound **195** as white crystals (31.5 mg, 64%), with a further fraction (14 mg, 28%) of slightly impure material.

R_f : 0.20 (ethyl acetate:hexane, 1:1). **IR** 1765, 1720 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (3H, s, H18), 1.20 - 2.80 (9H, m), 2.0 - 2.3 (3H, m), 2.42 (1H, dd, J_1 = 12.8 Hz, J_2 = 6.0 Hz, H9), 2.46 (1H, d, J = 10.8 Hz, H6), 2.62 (1H, t, J = 5.9 Hz, H13), 2.81 (1H, d, J = 10.8 Hz, H5), 3.66 (1H, dd, J_1 = 10.9 Hz, J_2 = 6.0 Hz, H3), 3.77 (3H, s, $-CO_2CH_3$), 3.93 (1H, t, J = 2.5 Hz, H15), 5.09 (1H, br s, H 17), 5.11 (1H, br s, H'17).

^{13}C NMR (75 MHz, $CDCl_3$) δ 12.7 (C18), 15.6 (C11), 29.5, 29.6 (C1, C2), 31.3, 32.0 (C12, C14), 36.7 (C13), 43.0 (C6), 51.3 (C9), 52.6 ($-CO_2\underline{C}H_3$), 54.5 (C4), 55.8 (C8), 58.2 (C5), 72.7 (C3), 77.8 (C15), 93.4 (C10), 109.2 (C17), 157.1 (C16), 175.0, 177.5 (C19, C7).

MS (EI) *m/z* 362 (M^+, 1%), 330 (20), 149 (50), 143 (50), 129 (18). 115 (17), 105 (20), 95 (20), 91 (50), 79 (35), 77 (35), 69 (40), 57 (58), 55 (100). **MS** (CI, NH_3) *m/z* 380(M^++18, 55%), 363(M^++1), 347 (50), 345 (100), 332 (50), 330 (85), 313 (45), 303 (35), 284 (25). **HRMS** (EI) *m/z* calcd for M^+, $C_{20}H_{26}O_6$: 362.1729; found 362.1730.

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APPENDIX

A LIST OF ALL NATURALLY OCCURING GIBBERELLINS

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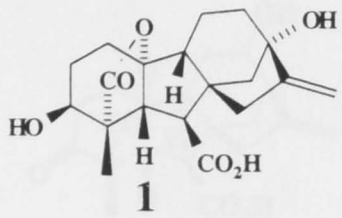
A LIST OF ALL NATURALLY OCCURING GIBBERELLINS



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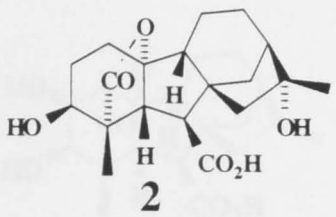

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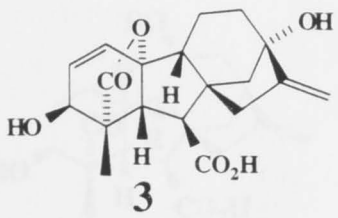

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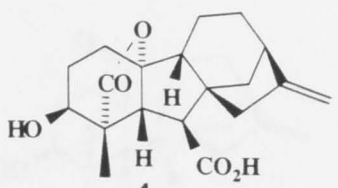

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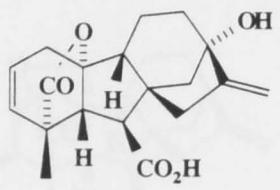

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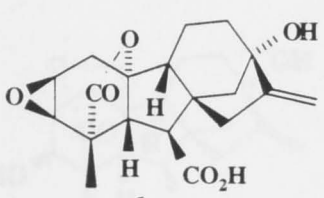

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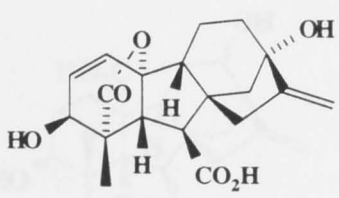

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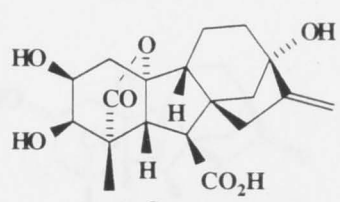

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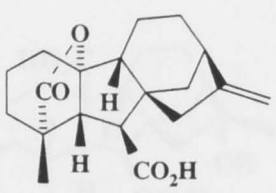

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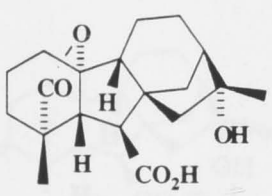

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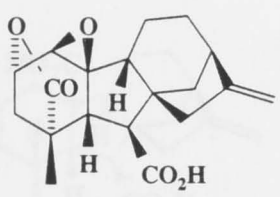

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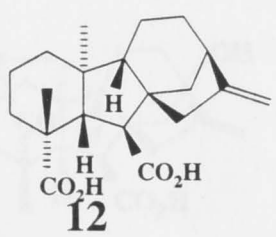

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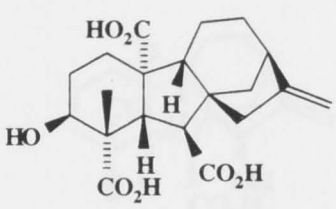

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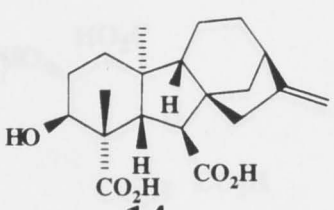

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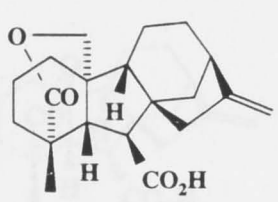

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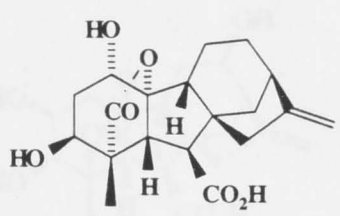

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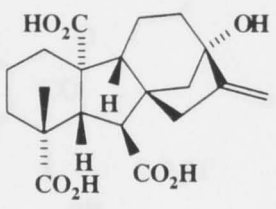

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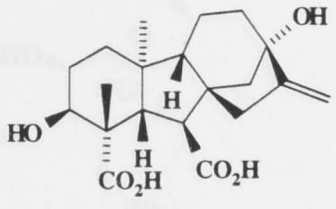

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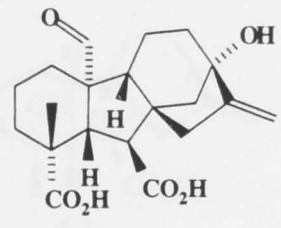

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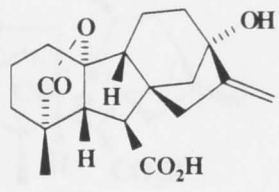

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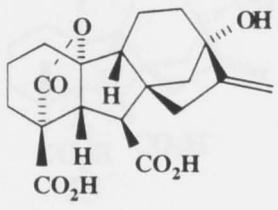

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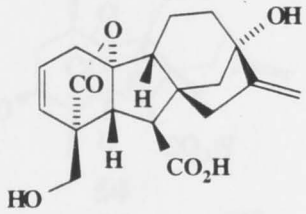

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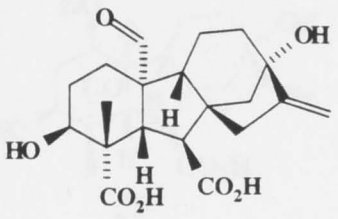

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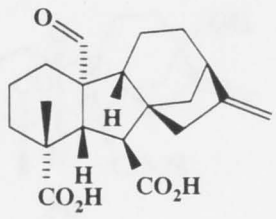

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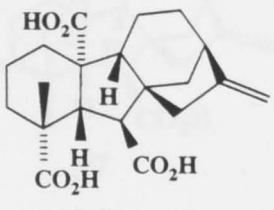

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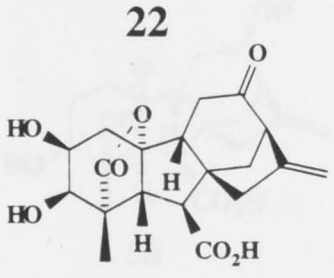

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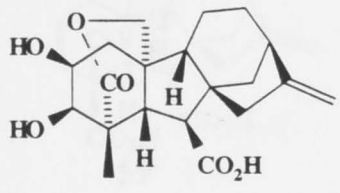

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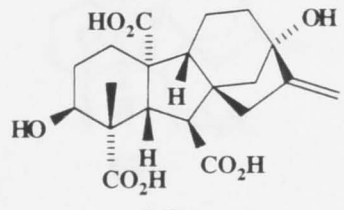

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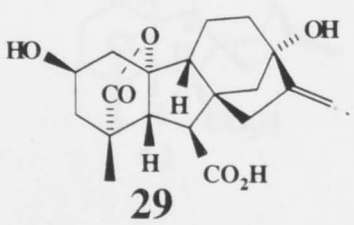

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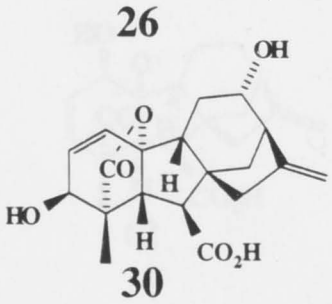

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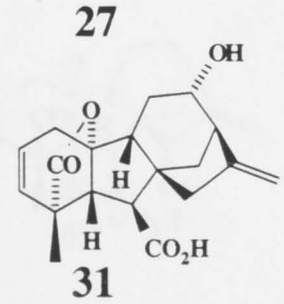

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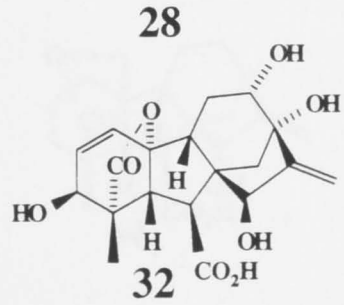

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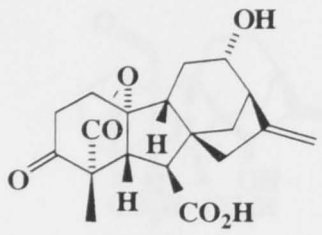

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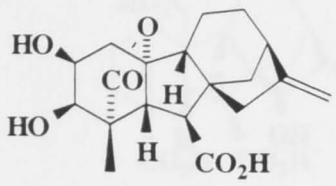

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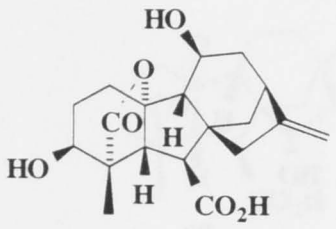

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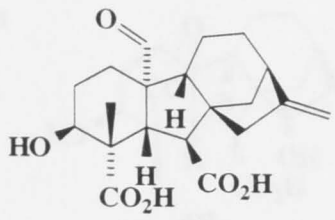

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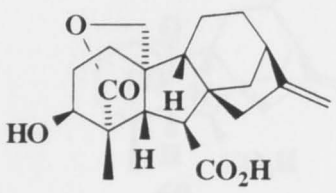

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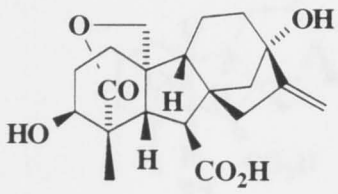

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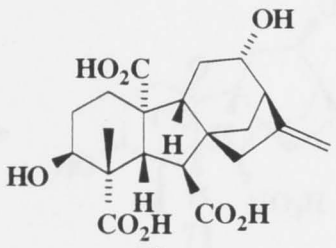

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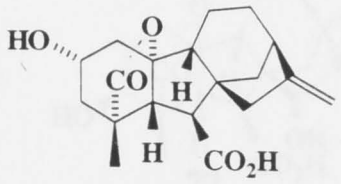

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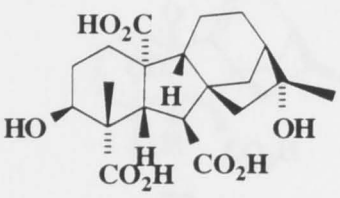

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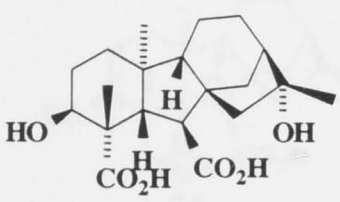

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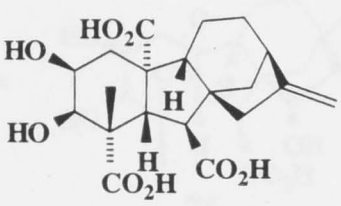

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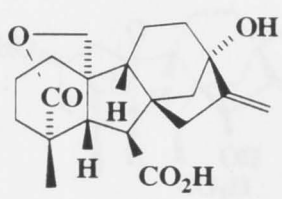

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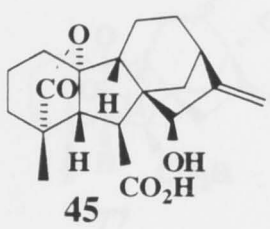

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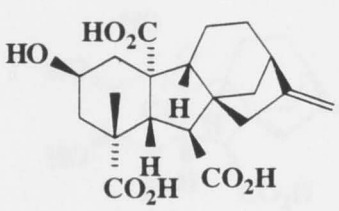

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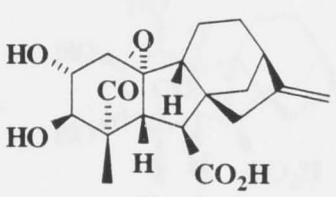

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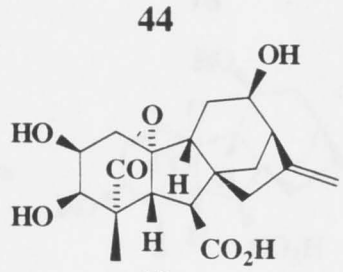

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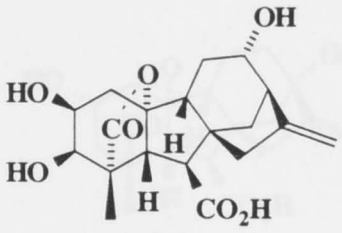

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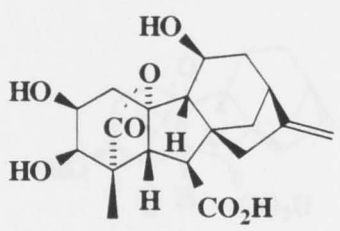

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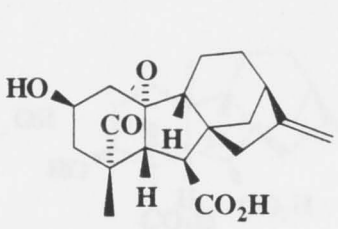

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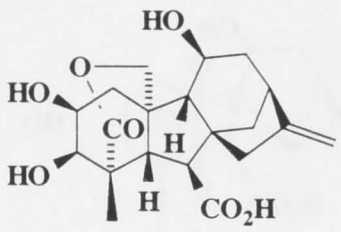

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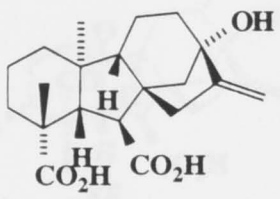

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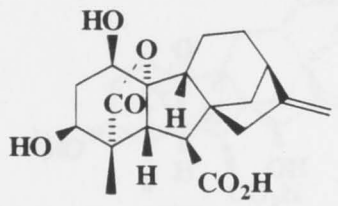

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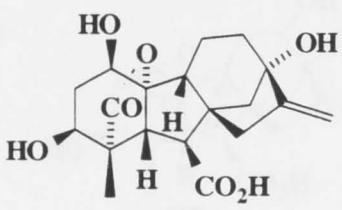

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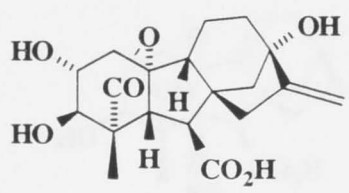

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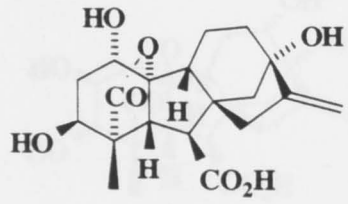

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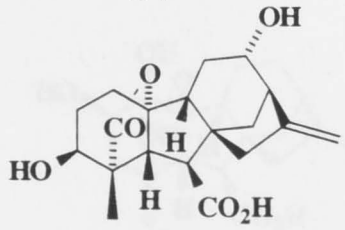

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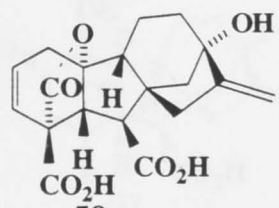

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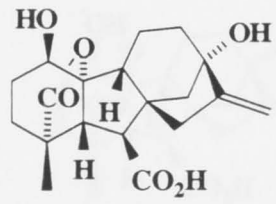

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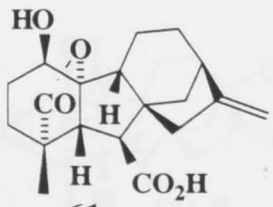

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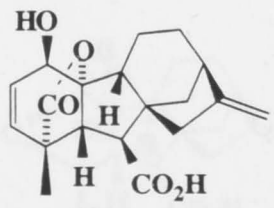

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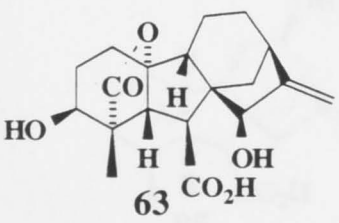

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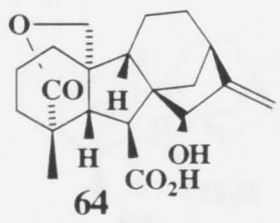

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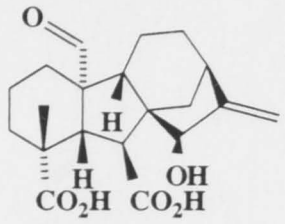

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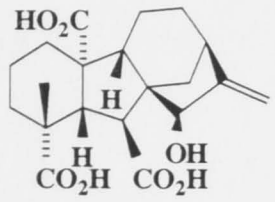

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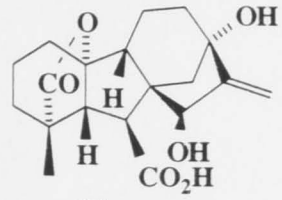

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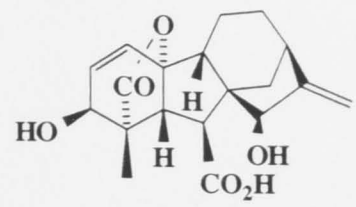

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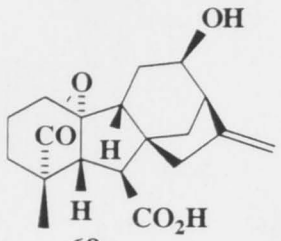

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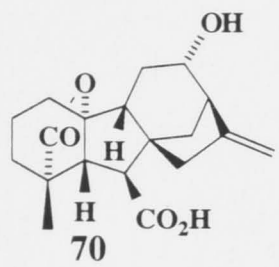

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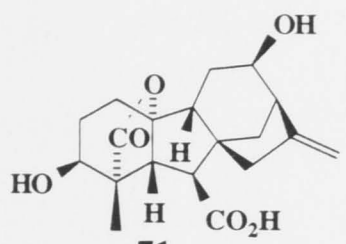

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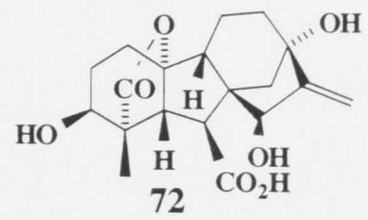

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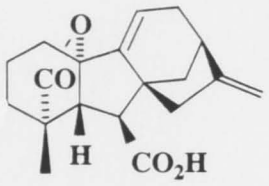

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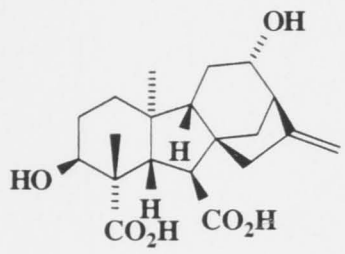

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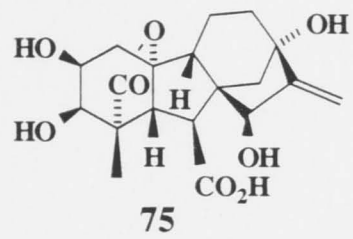

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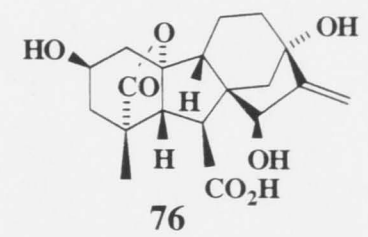

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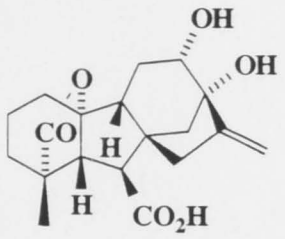

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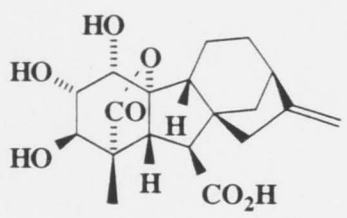

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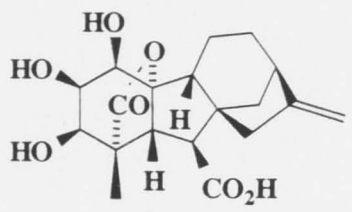

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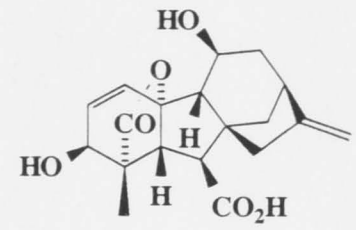

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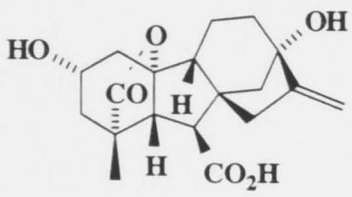

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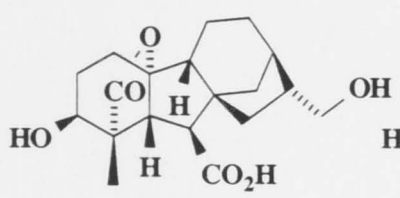

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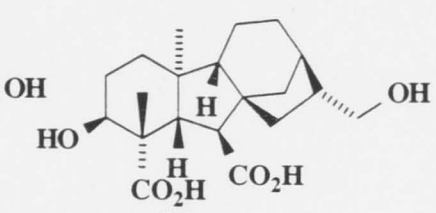

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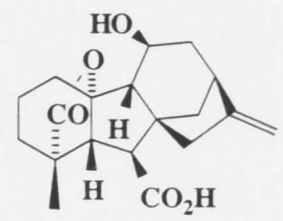

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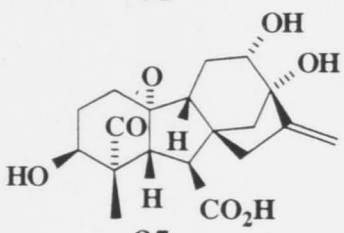

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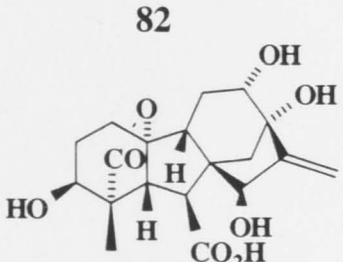

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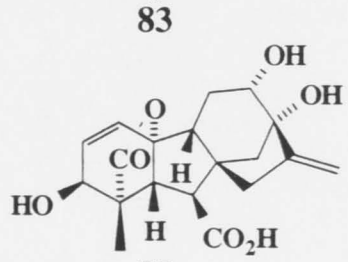

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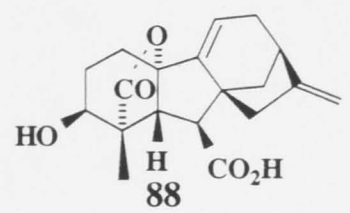

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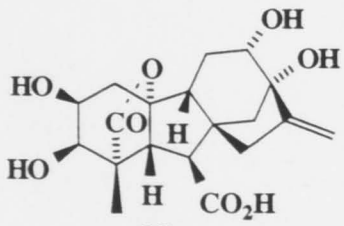

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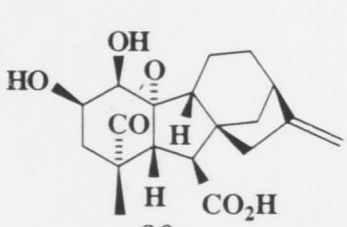

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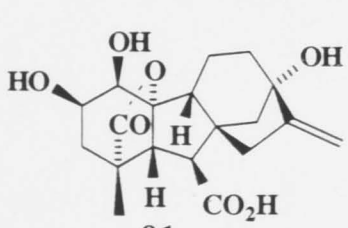

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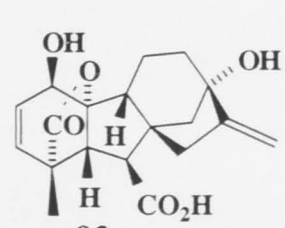

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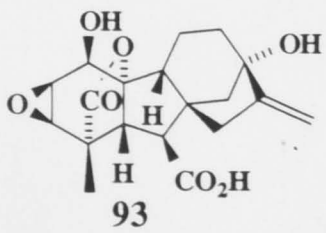

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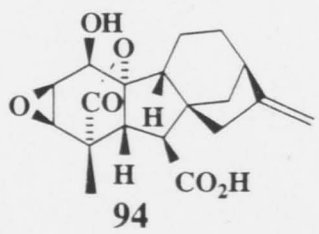

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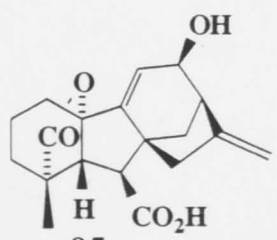

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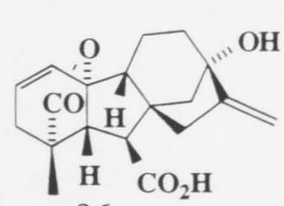

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